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THE SURGICAL TREATMENT OF MASSIVE LYMPHEDEMA OF THE LOWER EXTREMITIES

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CHRONIC lymphedema of the lower extremity is often a progressive disease which cannot be controlled by conservative measures. We have had a limited experience with the treatment of such cases by radical excision of the diseased tissues. The results have proved so satisfactory that we are encouraged to use this procedure in the treatment of additional patients. An etiological classification of lymphedema is presented in Table I.

TABLE I

Primary: developmental defect of lymphatics
1. Congenital lymphedema (idiopathic and familial)
2. Lymphedema praecox
Secondary: lymphatic obstruction
1. Malignancy
2. Excision
3. External pressure
4. Roentgen therapy
5. Infection

PATHOLOGY AND PATHOGENESIS

In severe chronic lymphedema there is a thickening of the skin and subcutaneous tissue, replacement of fatty tissue with enlarged lymph vessels and fibrous tissue, atrophy of the muscles, and infiltration of inflammatory cells. With lymphatic stasis a fluid which has a high protein content collects in the interstitial space. This edema fluid stimulates fibroblastic proliferation. The resultant fibrosis further contributes to the stasis and reduces resistance to infection. Additionally, there is a dilatation of the distal lymph vessels with subsequent insufficiency of the valves. Thus, there follows a vicious cycle consisting of obstruction, edema, fibrosis, and infection.

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A. *B.*

Fig. 1.—B. C., a 41-year-old Negro woman. *A*, appearance before operation; *B*, appearance 18 months after operation.

A. *B.*

Fig. 2.—D. C., a 40-year-old Negro woman. *A*, appearance preoperatively; *B*, appearance 14 months following operation.

In the three patients which we have treated by operation the lymphedema was due to obstruction (secondary group) caused by infection. The infection was a complication of previous venous thrombosis and thrombophlebitis.

In an effort to relieve patients of lymphedema, various types of operative procedures have been tried in the past. Scarification, excision of skin, and the subcutaneous implantation of fascia lata, silk threads, and other foreign materials have all proved inadequate. The first satisfactory results were obtained by the use of modified versions of the operation described by Kondoleon in

A. *B.*

Fig. 3.—J. R., a 42-year-old man. *A*, appearance before operation; *B*, appearance 15 months after operation.

1912.[1] Homans,[2] in 1936, introduced the idea of excision of the diseased subcutaneous tissue below the knee with preservation of skin for wound closure. Macy,[3] in 1940, and Poth, Barnes, and Ross,[4] in 1947, reported their experiences with excision of the skin as well as the subcutaneous tissues below the knee. Wound closure was accomplished by the use of split-thickness grafts obtained from other parts of the body. In 1949 Blocker[5] proposed a procedure similar to Poth's which we have followed closely.

OBJECTIVES OF SURGICAL TREATMENT

The indications for and objectives of operative treatment are to (1) improve function, (2) improve appearance, (3) restore employability, (4) reduce morbidity, and (5) prolong life.

CASE REPORTS

CASE 1.—B. C., a 41-year-old Negro woman, was admitted with a history of swelling of the right leg for twenty years following delivery of her first child. She had experienced increased swelling of the leg with each of nine pregnancies. A right lumbar sympathectomy had been carried out at the Ochsner Clinic four years previously. Examination revealed massive brawny lymphedema and ulceration of the right lower extremity. Fig. 1 shows her appearance before operation and eighteen months postoperatively. She now enjoys a relatively normal life except for recurrent episodes of infection. Extreme care of this leg is necessary to reduce the frequency of these episodes.

Fig. 4.—A diagram of the operative technique illustrating block excision of the diseased skin, subcutaneous tissue, and deep fascia followed by application of skin grafts. (Drawing by M. Shapiro.)

CASE 2.—D. C. is a 40-year-old Negro woman from whom no reliable history could be obtained. Examination revealed massive lymphedema of the right lower extremity with minimal ulceration. Fig. 2 shows her appearance before operation and fourteen months later.

CASE 3.—J. R. is a 42-year-old white man with a history of intermittent progressive swelling of both legs of four years' duration. Examination revealed massive lymphedema and ulceration of the left lower extremity. Fig. 3 shows his appearance before operation and fifteen months later. He is now working every day.

TECHNIQUE

Our technique for treatment has been the same in each of the cases (Fig. 4). The patient was confined to bed with the affected extremity elevated and

wrapped with compression bandages until no further decrease in size occurred. The leg was scrubbed daily with pHisoderm. Parenteral penicillin was administered preoperatively. At operation, with a pneumatic tourniquet applied, an incision was made from the tibial tuberosity to the base of the toes. The skin, subcutaneous tissue, and deep fascia were resected as a flap, leaving skin over the toes, the sole of the foot, and the Achilles tendon. Skin grafts 0.012 of an inch thick taken from the body and thighs were sutured into place. A massive pressure dressing was applied. The wounds were dressed on the eighth postoperative day and on the fourteenth day, with elastic support to the leg, the patient was allowed to get up.

CONCLUSION AND SUMMARY

1. We believe radical excision of the diseased tissues below the knee is a satisfactory method of treating severe chronic lymphedema.

2. Three patients with severe lymphedema treated in this manner have been presented.

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CHRONIC PORTAL VEIN OCCLUSION AND PORTAL HYPERTENSION IN THE DOG

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SHUNTING the portal blood to the systemic veins for the purpose of diminishing portal hypertension by splenorenal or portacaval anastomosis is currently being applied with apparent good results in the treatment of patients who have had hemorrhages from esophageal varices.[3, 4, 8] Whether a permanent reduction in portal venous pressure can be produced is not known since there is no practical method for determining portal pressure in the human subject by direct measurement after these shunts have been performed. Thus the only indication of a lasting reduction in portal pressure is the cessation or the decreased frequency of gastrointestinal hemorrhages from esophageal varices. Although this latter evidence is sufficient to warrant the employment of portacaval shunts in selected cases of portal hypertension, a knowledge of the long-range portal pressure changes that might be expected would be most valuable in determining the efficiency of the procedure. It is apparent that an experimental preparation of animals having portal hypertension would allow us to make valuable observations on the efficiency of various shunts as to degree of reduction in pressure, the probability of thrombosis, and effects on existing collaterals. We have attempted to produce portal hypertension in dogs by extrahepatic obstruction of the portal venous system.

Complete one-stage ligation of the portal vein in dogs leads almost uniformly to death within twelve hours with congestion and venous infarction of the viscera. It was established by Tilmann[16] that death can be avoided and survival obtained after total portal vein occlusion in dogs if complete ligation is delayed for at least eight days after preliminary partial occlusion of the vein to one-half of its diameter. Monkeys and possibly other animals, however, can sustain complete sudden ligation of the portal vein without ill effect.[11] Gradual constriction of vessels to a degree that complete occlusion is possible can be effected by producing gradual fibrosis about an artery or vein.[5] The first use of reactive Cellophane for constricting arteries was described by Pearse.[13] Whipple[17] reported that Rousselot and Rennie produced portal hypertension in 50 per cent of a group of dogs in which the portal vein was occluded by using the Cellophane technique.

Gradual occlusion of the portal vein has been carried out by us in a series of experiments using reactive polyethylene (Dupont) as the fibrosing agent in the experiments about to be reported. In addition, we have tried to attain

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higher portal venous pressures by means of an arteriovenous fistula between the renal artery and the splenic vein. It was hoped that the stimulating effect on the venous collaterals by an arteriovenous fistula might produce extensive esophageal varices as well as portal hypertension. Renal artery-splenic vein fistula, according to Markowitz,[10] was first used by Narath[12] in order to provide arterial blood for the liver of dogs whose hepatic arteries had been ligated. Recently, introduction of arterial blood flow into the portal system has been reported by Schilling and associates,[15] who inserted the hepatic artery into the portal vein lumen without sutures and without dividing the portal vein. In three successful arteriovenous fistula preparations they found at re-exploration portal vein pressures of between 14.8 cm. and 20 cm. of water, which are not significantly elevated values.

Ligation of all the venous drainage of the stomach, except for the veins at the cardio-esophageal junction, has been performed by Baronofsky and Wangensteen[1] in an attempt to produce a regional elevation of tension in the venous system sufficient to cause esophageal varicosities and mucosal ulceration with bleeding of the varices in their experiments. Similar ligations were undertaken by us in conjunction with complete portal vein ligation procedures.

METHODS AND RESULTS

Venous pressures in the portal system were measured in eight control dogs at laparotomy under pentobarbital anesthesia. The pressures were determined immediately after the abdomen was opened, utilizing a simple water type of manometer filled with citrated saline solution. The manometer was placed so that the zero mark was level with the portal vein entering the liver and was joined by a fluid-filled rubber tube to a 20 gauge needle inserted into a superior mesenteric tributary. The pressures obtained in the superior mesenteric vein are tabulated in Table I. They ranged from 9 to 15 cm. of water; the average pressure was 12 cm. Pressures taken in the gastric veins were slightly less and averaged 10.6 cm. of water.

TABLE I. PORTAL PRESSURES IN NORMAL DOGS UNDER PENTOBARBITAL ANESTHESIA AT LAPAROTOMY

DOG NUMBER	MESENTERIC VEINS (CM. WATER)	GASTRIC VEIN (CM. WATER)
9	14	13
10	9	9
12	13	9.5
13	9	8
14	15	12.5
15	12	12.5
16	13	12
17	12	8.5
Average	12.1	10.6

In fourteen dogs the portal vein was successfully divided in multiple stages and portal system pressures were determined at intervals after the occlusion. First, the portal vein was dissected free at the area just proximal to entrance into the liver. A band of Dupont reactive polyethylene film 0.5

cm. to 1 cm. wide was wrapped about the vein, constricting it sufficiently to allow only the insertion of the tip of a pair of forceps about 2 mm. in diameter between the polyethylene band and the vein. This band was tied and secured with a suture or a cotton tape. The recognizable potential collateral veins in this region were then divided, including the coronary vein, which often joined the portal vein at this point. In addition, a large pyloric branch of the portal vein coming from the duodenum and pancreas and the collateral veins lying in the gastrohepatic ligament and hepatic pedicle were ligated when present. After three to four weeks the sclerosing process produced a gradual occlusion of the vein. At the second operation, the portal vein was isolated and temporarily constricted. Providing there was no marked change in the portal pressure, the vein was divided. In some cases severe portal venous congestion at this stage precluded safe ligation and it was necessary to further constrict the vein, reserving division until a third exploration. Exploratory laparotomy was then performed three or more weeks following complete division of the portal vein, and portal venous pressures were redetermined. These pressures in the superior mesenteric vein were found to vary between 13 cm. and 22 cm. of water, with an average value of 16 cm. as recorded in Table II.

TABLE II. PORTAL VENOUS PRESSURES FOLLOWING OCCLUSION OF PORTAL VEIN IN STAGES (GROUP 1)

DOG NUMBER	INTERVAL AFTER LIGATION (WEEKS)	MESENTERIC VEINS (CM. WATER)
1	3	17.5
2	4	22.0
3	3	18.0
4	5	18.0
5	28	17.5
6	4	17.0
7	3	17.0
8	24	17.5
10	5	14.0
11	4	14.0
12	4	13.0
13	5	11.0
14	4	14.0
17	4	14.0
Average		16.1

In a group of dogs with the portal veins previously ligated and divided by the multiple stage method, arteriovenous fistulas were created between the left renal artery and one of the main divisions of the splenic vein. Venous drainage of the spleen was preserved by means of the intact smaller splenic vein branches. The left kidney was removed and an end-to-end renal artery to splenic vein anastomosis was then performed using either a silk suture technique or the nonsuture method employing Vitallium cuffs described by Blakemore and Lord.[3] Portal system pressures taken immediately after completion of the fistula anastomosis were found to vary between 24 and 58 cm. of water. These values were not considered to be representative, however, because at this time the animals frequently had arterial hypotension with the opening of the fistula

and the veins were often in spasm. A thrill could be felt following completion of the anastomosis, and in most cases a definite murmur could be heard on auscultation at the left flank postoperatively. One nonsuture anastomosis became thrombosed and the other reduced to an inadequate lumen of 1 mm. Three of the five suture anastomoses maintained adequate patency. The pressures in the superior mesenteric vein taken in those animals with patent fistulas after four to eight weeks varied between 17 cm. and 26 cm. with an average of 19.5 cm. of water (Table III).

TABLE III. PORTAL VENOUS PRESSURE FOLLOWING RENAL ARTERY-SPLENIC VEIN FISTULA WITH OCCLUDED PORTAL VEIN

DOG NUMBER	WEEKS AFTER FISTULA MADE	VEIN MEASURED (CM. WATER)		TYPE ANASTOMOSIS	REMARKS
3	6	Splenic	22.0	Vitallium cuff	1 mm. patency
		Mesenteric	16.5		
4	6	Mesenteric	20.5	Vitallium cuff	Occluded at autopsy
7	4	Splenic	24.0	Suture	Patent at operation
		Mesenteric	17.0		
7	8	Gastric	15.0	Suture	Patent
		Mesenteric	26.0		
9	20	Mesenteric	16	Suture	Occluded
10	13	Mesenteric	16.25	Suture	Occluded
12	5	Mesenteric	12.5	Suture	Occluded
13	4	Mesenteric	18.5	Suture	Patent at autopsy
		Gastric	18		

In another group of dogs venous pressure studies were made in the cardio-esophageal region in which segmental occlusions of the portal system draining this region were carried out. The coronary vein of the lesser curvature of the stomach, the left gastro-epiploic vein at the greater curvature of the stomach, and the splenic vein proximal to the entrance of the inferior mesenteric vein were ligated and divided. The corresponding arteries were not disturbed. This procedure was followed immediately by acute congestion and distention of the spleen, causing difficulty in wound closure but apparently with no late ill effect. Venous pressures taken four weeks to five months later at the cardia of the stomach did not differ significantly from the normal values obtained simultaneously in the mesenteric and the portal veins. No dilated esophageal veins or varices were found at reoperation or autopsy. Enlarged collateral veins observed bridging the ligated gastro-epiploic and splenic vessels appeared to provide adequate venous drainage.

To demonstrate the functioning collateral venous channels Diodrast or Thorotrast was injected into the splenic or mesenteric veins of anesthetized animals who had previously had portal vein ligation. These venograms showed the radiopaque substance passing readily in each instance through extensive venous collaterals in the mesentery to the vena cava, filling all lobes of the liver, the azygos vein, the lumbar veins, and even the vertebral veins (Fig. 1).

Post-mortem examinations were performed at the time of death or sacrifice of the animal in order to study the venous collaterals. The anatomy of the portal circulation has been well described[9]; however, in our group, there

was usually only a moderate dilatation of the superficial epigastric veins of the abdominal wall with no true caput medusa. Dilated veins of Retzius in the mesenteries of the colon and duodenum drained the portal circulation via enlarged lumbar veins into the vena cava. The azygos veins receiving blood from these collaterals were also consistently enlarged. The veins about the stomach were somewhat larger than normal, but their increase in size did not approach those of the mesenteries of the duodenum and colon. In spite of previous regional ligations, enlarged branches of the coronary vein of the stomach were frequently found extending to the distal stump of the portal

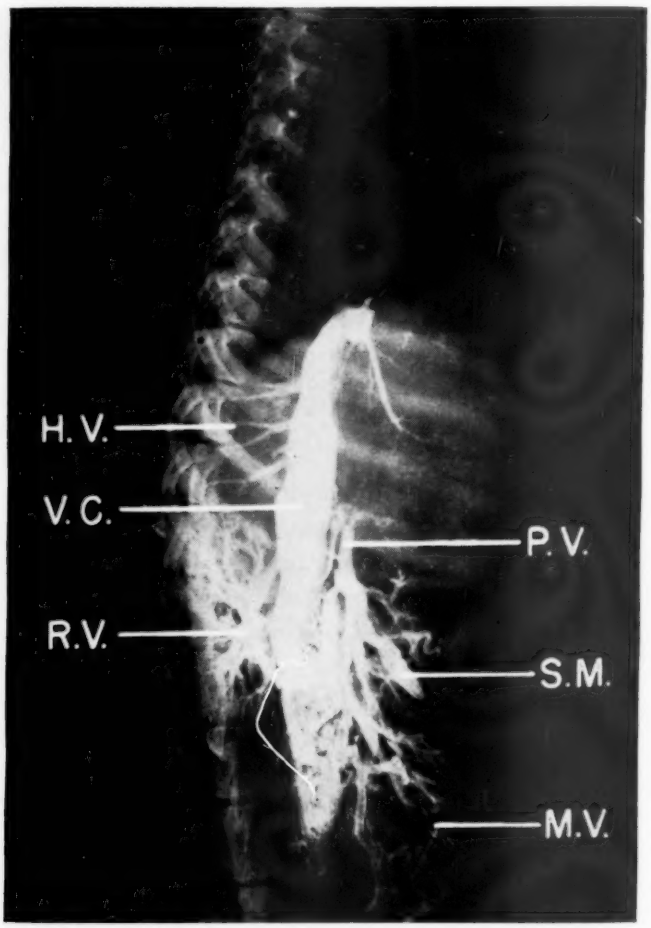

Fig. 1.—Venogram following Diodrast injection of the portal system through a cannula in the superior mesenteric vein (S. M.). The ligated proximal stump of the portal vein (P. V.) is shown. Free flow to the vena cava (V. C.) is demonstrated with filling of the right renal vein (R. V.) and the hepatic veins (H. V.). There is retrograde filling of the mesenteric veins (M. V.).

vein at the liver edge. The right gastro-epiploic vein was unchanged except for sharing in the moderate increase in size of the associate splenic and the short gastric veins. Dilated submucosal esophageal veins or varices were particularly sought but not found. Two enlarged periesophageal veins were consistently observed rising superiorly from the cardiac portion of the

stomach where they anastomosed with the veins of the stomach. These veins accompanied the vagus nerves superiorly and drained into the azygos veins in the posterior mediastinum to the vena cava. The enlarged collateral channels in the animals having splenorenal arteriovenous fistulas were of identical pattern to those of animals with only portal vein ligation, but were developed to a somewhat greater extent.

In an attempt to eliminate the portal system collaterals emptying into it, the inferior portion of the vena cava below the renal veins was ligated in one preparation. The dilated veins adjacent to the ureters and enlarged lumbar branches appeared to provide an ample bridge across the divided vena cava. This procedure was without effect on the portal venous pressure.

After portal vein ligation the spleen was found to be smaller than normal at exploration. A white fibrous capsule which microscopically was consistent with perisplenitis was usually present, but parenchymal fibrosis as seen in Banti's disease was never observed. Most of the animals developed anemia and malnutrition after several weeks.

DISCUSSION

Many attempts to produce elevated portal venous pressures in dogs have been reported by others. Kershner and associates[7] caused ascites to occur in the dog by ligating the vena cava above the renal veins in two stages, following this with partial constriction of the inferior vena cava above the diaphragm. The portal pressures, however, obtained by them were in the range of 15 cm. of water. Rousselot and Thompson[14] reported apparently the most successful experimental elevation of portal venous pressures in dogs which they accomplished by producing cirrhosis of the liver through the repeated injections of finely divided silicon dioxide into the splenic vein. The portal venous pressures resulting from the intrahepatic block were reported as high as 47 cm. of water and a congested type of spleen was described. For their method it was necessary to subject these animals to numerous laparotomies for the series of injections over a period of about twenty-four months. This method would be time consuming and introduces the factor of liver damage which might complicate experiments designed to investigate the effects and the treatment of portal venous hypertension.

The normal portal pressures in the dogs of the present series were slightly higher than the values reported by Hoffbauer.[6] This may be explained in part by the fact that the determinations in the present experiments were made with the abdomen opened under general anesthesia. After complete occlusion of the portal vein the pressures were elevated to values of only 13 to 22 cm. with an average of 16.1 cm. of water. None of these pressures equalled the values observed by Blakemore and Lord[3] in human cases of portal hypertension; they reported elevated pressures of from 25 cm. to over 50 cm. of water at operation. Our pressures remained almost within the normal human range of 14 to 22 cm. of water[2] and were not sufficient to produce congestive splenomegaly, esophageal varices, and other features seen with increased portal pressure in human beings. The reason for failure to develop high portal pressures in our experiments was

apparent when the animals were examined at autopsy. The remarkable prominently-developed collateral venous channels provided adequate egress for the portal circulation to the caval veins in spite of the increased load of arterial blood by the renal artery-splenic vein fistula. Similarly, local areas of venous hypertension did not develop at the gastric cardioesophageal junction after segmental venous occlusion.

SUMMARY

1. Chronic extrahepatic portal vein occlusion does not produce significant portal hypertension in the dog.

2. In dogs the main collateral venous drainage of the portal system is through the lumbar and azygos veins via venous channels of the mesentery of the intestine.

3. Introduction of the systemic renal arterial pressure into the portal system by means of an arteriovenous fistula increases the size of venous collaterals but does not produce satisfactory portal hypertension or esophageal varices.

4. Simultaneous ligation of the splenic vein, left gastric vein, and left gastro-epiploic vein does not produce an appreciable segmental or local venous hypertension of the cardia of the stomach.

5. Extrahepatic portal hypertension comparable to that seen in human subjects cannot be produced in the dog by the experimental methods used.

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OBSERVATIONS ON THE COMPLETE REVERSAL OF THE CIRCULATION IN THE HIND LIMB OF THE DOG

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THE delivery of arterial blood to the tissues through venous channels has been advocated as a method to improve the circulation in cases of arterial disease involving the peripheral,[1] the coronary,[2] and the cerebral vessels.[3] There has never been clinical agreement as to the efficacy of the procedure. Proof that the operation is physiologically sound is still lacking because of inadequate evaluation of the hemodynamic changes which occur when the blood flow is reversed.

Several inherent difficulties will be met when an attempt is made to reverse the circulation through the capillary bed. In venous systems with valves, blood under arterial pressure must overcome the resistance of the valves. Carrel and Guthrie[4] observed that after a time this resistance could be overcome. When communicating veins are present, arterial blood might be shunted into low pressure areas, thereby diminishing the pressure exerted against the valves. In systems without valves but with patent communicating veins, most of the arterial blood might pass via the communicating veins back to the heart, by-passing the capillary bed. The ability of the venules to withstand arterial pressure and the ability of the arterial bed to drain the capillary bed adequately are other important considerations. Landis and Hortenstine[5] have called attention to the fact that the venous bed is nearly four times as large as the arterial bed.

To investigate the effects of the delivery of arterial blood to the tissues by the venous circulation the following experiments were performed.

METHODS

The femoral circulations in ten adult mongrel dogs were utilized. Glass cannulas were devised to facilitate the delivery of arterial blood directly from the femoral artery to the femoral vein and to return the venous blood by the distal arterial system to the femoral and iliac veins. Side arms on the cannulas were utilized to obtain flow and pressure measurements. The dogs were anesthetized with intravenous Nembutal, 40 mg. per kilogram of body weight. An infusion of normal saline solution was started in the jugular vein at the beginning of each experiment. Incisions were made in each femoral triangle, and the femoral vessels isolated and divided. In one thigh the special cannulas were inserted so as to shunt arterial blood into the venous system and allow the distal artery to drain the capillary bed back to the abdominal venous

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system. In the other thigh, used as a control, straight cannulas with side arms reconnected artery to artery and vein to vein. All bleeding points were meticulously ligated and heparin,* 10 mg. per kilogram, was injected intravenously. The circumference of the upper and lower leg was measured at a fixed point above the nearest bony prominence. Intra-arterial and intravenous pressures were taken with an exploring needle which recorded on a Sanborn electromanometer and visocardiette. The blood flow from the limb was measured by diverting the return blood through the side arm into a graduate cylinder. After adequate control periods the collateral circulation of both legs was occluded at the same time by tightening lengths of piano wire about the thigh so as to compress all the tissues other than the femoral vessels. Observations were then made on the resultant alterations in peripheral hemodynamics.

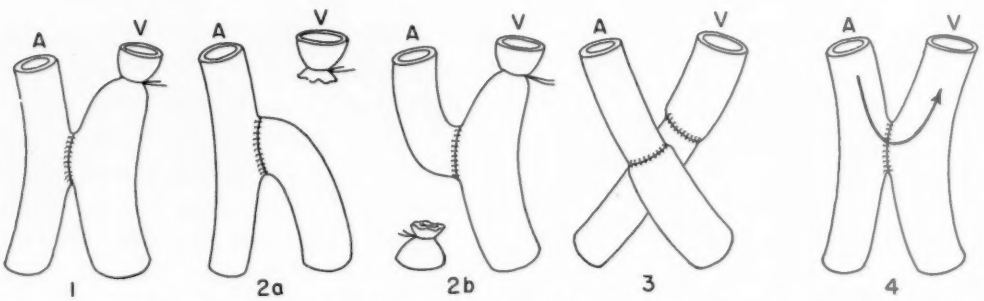

Fig. 1.—An illustration of the various methods advocated for reversal of the circulation. *1*, Side-to-side arteriovenous anastomosis with ligation of the cardiac end of the vein; *2a*, end-to-side vein-to-artery anastomosis; *2b*, end-to-side artery-to-vein anastomosis; *3*, cross anastomosis of both artery and vein; *4*, simple arteriovenous fistula.

RESULTS

The first observations made were those after circulation reversal on one side, but prior to application of the tourniquets. There was no change in the external appearance of either limb. Uniformly the returning blood flow on the experimental side was greater than on the control side, averaging 116 c.c. per minute as compared to 77 c.c. per minute. The returning blood on the experimental side was always arterial in color, as contrasted with reduced blood in the control limb. The paw was cooler on the side of circulation reversal. Fig. 2 shows the averages of the existing pressure relationships. In seven experiments values for distal arterial pressure were comparable to abdominal venous pressure. Pressures in the distal venous system were higher than abdominal venous pressure, but much lower than arterial pressure (42 mm. Hg compared to 139 mm. Hg). During this time no change in limb circumference developed.

Next the tourniquets were applied to occlude all but the femoral vessels. Under these conditions strict criteria for circulation reversal were brought into effect. When the tourniquets were tightened on the experimental side the blood returning via the distal artery abruptly darkened in color, and

*Liquamin. Hoffmann-La Roche.

volume flow dropped from an average of 116 c.c. per minute to 6 c.c. per minute. A tourniquet about the control limb made no difference in the blood color and return flows remained essentially the same (72 c.c. per minute before and 63 c.c. per minute after). Fig. 3 (average figures) shows the readjustment in pressure relationships in the seven animals. There was a slight rise in systemic systolic blood pressure which was maintained for the rest of the experiment. On the experimental side the pressure in the distal venous system immediately began to rise and continued to do so throughout the remainder of the observation time (about 3 hours for each experiment). The average

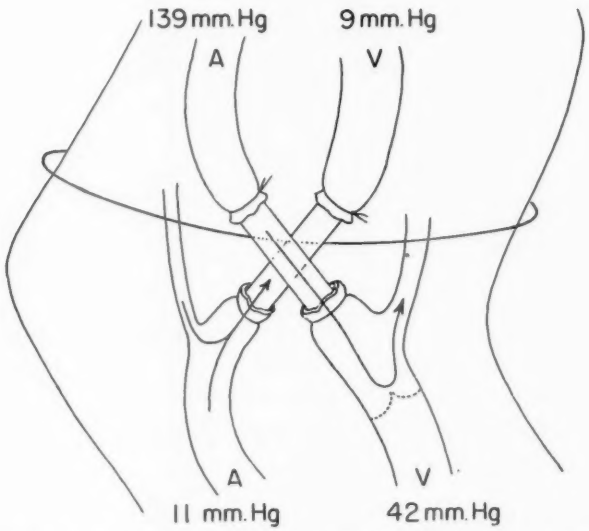

Fig. 2.—Illustration of cross anastomosis of artery to vein by glass cannulas with collateral circulation patent. Arrows show the direction of blood flow. Pressure notations represent average readings in seven dogs.

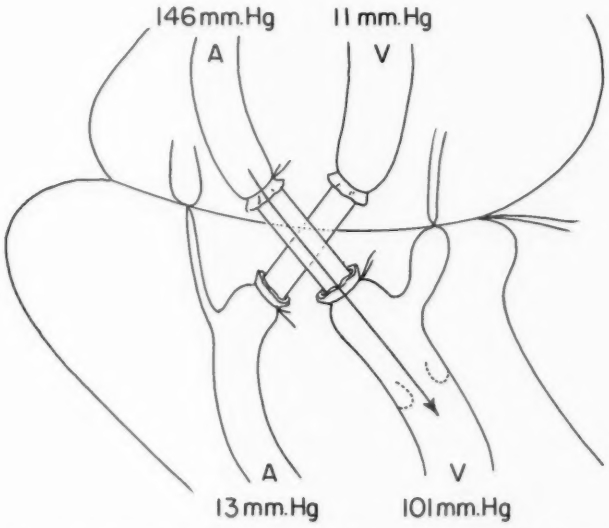

Fig. 3.—Illustration of cross anastomosis of artery to vein by glass cannulas with collateral circulation occluded by a wire tourniquet. Pressure represents average readings in seven dogs.

rise was 101 mm. Hg, although in several experiments the venous pressure reached an equilibrium with arterial blood pressure. With the pressure rise there was a progressive swelling of the limb. At the end of two hours the extremity was massively engorged, the skin was colored a deep purple, and the cut surfaces oozed thin bloody fluid. The average increase in thigh diameter was 3.9 cm. There was no swelling of the control limb except in one experiment when the femoral vein was clamped, and then the limb became engorged at a rate comparable to the experimental side.

Two animals deviated markedly from this pattern. In contrast to the other seven experiments, after tourniquet application the limbs with the reversed circulation became pale, there was no swelling, and the skin was cool. These conditions persisted well over an hour in each experiment. The cause in each case was found to be a valve just distal to the cannula tip which was competent under full arterial pressure and allowed no blood to pass into the distal venous bed. The distal venous pressures were only 30 mm. Hg instead of the expected 100 mm. Hg or above as in the other experiments. By manipulation of the valve area with tweezers, the cusps could be forced to give away with resultant rise in venous pressure and swelling of the limb.

Studies were done with segments of veins at the completion of several experiments. All collaterals were clamped, and saline solution was injected in a retrograde manner into the vein segment. Nonpulsatile pressure required to force the valves varied from 90 mm. Hg to 300 mm. Hg. Incompetence could be obtained at a lower pressure if manipulation of the segment was done at the same time.

DISCUSSION

To appraise the problem of circulation reversal, evaluation must be made under two sets of circumstances, that is, with the collateral circulation patent and with it occluded. Prior to application of the tourniquet, the presence of oxygenated blood in the return flow and the higher than control figures for volume return indicate that there is considerable shunting of blood from collateral arteries into the femoral artery and thence through the femoral vein to the heart. This makes less total arterial blood available for tissue perfusion, as was substantiated by the lowered paw temperatures. In addition, the arterial stream which is diverted into the venous bed still has two forces to overcome before reaching the tissues, the valves and the communicating veins. Our observations show that the venous valves in some instances are remarkable in their ability to withstand high pulsatile pressures. Then, when the valves do become incompetent the blood will preferentially pass into collateral veins and back to the heart rather than to the tissues. These observations are similar to those of Horsley and Whitehead[6] and Stetten.[7] It is impossible to say just how far down the venous system the arterial blood can travel, but with collaterals open it is highly unlikely that any significant amount reaches the level of tissue nutrition. Such a preparation really represents a modified arteriovenous fistula rather than a reversal of the circulation.

With occlusion of the collateral circulation a more accurate attempt is made to force the flow of blood in a retrograde manner. Here again the valves may still offer resistance, and in two instances out of nine a single valve was able to withstand full arterial pressure. With the gradual forcing of valves and without the drain-off effect of the communicating veins, the venous system is soon filled to capacity, and intravenous pressure begins to rise. In time, almost full arterial pressure may be thrown against the venules. It will be recalled in normal blood flow that this area is cushioned from these effects by the pressure drop across the arteriolar resistance (100 mm. Hg to 25 mm. Hg) and by a further drop across the capillary (25 mm. Hg to 12 mm. Hg). The venocapillary membrane is thus subjected to very little pressure. When circulation reversal is attempted no such cushioning mechanism is present, and high pressures reach the venules. Extravasation of blood and fluid occurs. Although this mechanism is most marked when collaterals are occluded and valves are functionless, it presumably would occur in any case where a large enough volume of blood reached the venules to elevate the intravascular pressure.

These results in part explain the difficulties that have been encountered when reversal operations have been tried clinically. In the case of the femoral system the combination valvular resistance and patent communicating vessels makes it unlikely that arterial blood would ever reach the smaller veins, even less the capillaries. This would indicate that the reversal procedure is not a physiologically sound method of improving tissue nutrition in the extremity. The discouraging results reported in attempting to save arteriosclerotic limbs seems to bear this out.[6, 7] In circuits where venous valves do not exist, such as the coronary and cerebral circulations, the observations suggest that careful regulation of the pressure which is allowed to reach the venocapillary is of prime importance. If it cannot be regulated, fluid will be forced out through the capillary wall instead of into the arterial system, and interstitial edema will be the consequence. There is already evidence that this factor may be a limiting one in arterialization of the coronary sinus.[2, 9] Also, increased intracranial pressure and cerebral edema are serious complications of carotid-jugular anastomosis,[3] and occur when there is not careful regulation of the size of the anastomotic opening.

SUMMARY

1. Reversal of the femoral circulation in the dog has been considered from the standpoint of inclusion and exclusion of the arterial and venous collateral channels.

2. With the collateral channels patent, the resistance to arterial flow offered by the venous valves and the bleed-off effect of the venous collateral vessels made an adequate perfusion of the capillary bed in the reverse direction impossible.

3. With the collateral channels occluded the valve obstruction is overcome, but because of the lack in the venous bed of a resistance comparable to the

arteriolar resistance, a high pressure is transmitted to the capillaries, where it causes extravasation of fluid.

4. The clinical implications of these findings are discussed.

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A SIMPLE ELECTRICAL APPARATUS FOR THE CLINICAL TREATMENT OF VENTRICULAR FIBRILLATION

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INTRODUCTION

THE successful treatment of cardiac arrest which occurs in the form of ventricular fibrillation depends upon the defibrillation of the ventricles and restitution of a good heartbeat. The only consistently successful clinical method of defibrillation is by electrical means. This method is not new; it was first described in 1899 by Prevost and Battelli.[1]

In 1949 Beck and Rand[2] stated that they had successfully electrically defibrillated the ventricles of the heart in two patients, both of whom recovered completely. In one of these patients cardiac arrest had been present for one hour and ten minutes (Beck, Pritchard, and Feil[3]).

In 1950 Southworth, McKusick, Pierce, and Rawson[4] reported the successful electrical defibrillation of a case of ventricular fibrillation which occurred during cardiac catheterization. The heart was defibrillated on the seventh attempt, after forty-five minutes of cardiac arrest, and the patient recovered completely.

In 1951 Johnson and Kirby[5] reported the successful electrical defibrillation of the heart in eight patients, four of whom recovered.

Two patients with ventricular fibrillation occurring during surgery have been treated successfully by electrical defibrillation at The Johns Hopkins Hospital. Both recovered completely without evidence of neurological changes. Cardiac arrest had been present for fifteen minutes in one case and five minutes in the other.

APPARATUS

The following apparatus is used for the treatment of ventricular fibrillation in The Johns Hopkins Hospital operating rooms. Requests for details of its construction have occasioned this description.

Power Unit.—The components of the power unit are: an isolation transformer, which separates the grounded power source from the current supplied to the electrodes; a variable voltage transformer called a variac, which is usually set at 130 volts; a foot switch for controlling the application and duration of the defibrillating shock; a convenience outlet or receptacle into which the plug attached to the electrode cord is inserted; a pilot lamp, which lights when the foot switch is pressed if all is in working order. This equipment is mounted on

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the base of a box. This box resembles the case of a portable typewriter and when the catches are released, the top, sides, and ends lift off leaving the power unit exposed (Fig. 1).

The isolation transformer is a 600 watt transformer with a ratio of 120 volts primary to 120 volts secondary. Its primary winding is completely insulated and separated from its secondary winding. The primary side of this transformer is provided with a cord of sufficient length to reach a convenient

Fig. 1.—Electrical defibrillator.

wall receptacle in the operating room. This receptacle should be supplied with a source of 120 volt, 60 cycle, alternating current. It is standard practice to connect all power supply systems to the earth. The isolation transformer effectively separates the output derived from the secondary winding from the ground connection. This eliminates the possibility of the surgical team's receiving an electrical shock, and eliminates the hazard of a spark when using the equipment in the operating room. The secondary terminals of the isolation transformer are connected to a convenience receptacle mounted on the transformer case. Isolation transformers are standard equipment and may be purchased from radio supply houses.

A 5 ampere, 0 to 135 volt variac is recommended. The variac we use is manufactured by the General Radio Company.* It is a continuously variable voltage transformer whose output voltage may be adjusted from 0 to 135 volts by turning a knob. The variac is connected to the secondary receptacle of the isolation transformer. The output circuit of the variac should contain a fuse to protect the equipment in the event that the electrodes are accidentally short-circuited. The output voltage of the variac is set at the 130 volt value for electrical defibrillation.

The output of the variac transformer is connected to a foot switch which is operated by the surgeon. This switch is of strong construction so that it will not break if a considerable force is exerted upon it. The type of foot switch which is most satisfactory is a completely enclosed switch manufactured by the General Electric Company and catalogued as a CR 2940-NH 101 Push Button Station. A 1 inch hole is drilled into the case of the foot switch. This hole is sealed with a rubber stopper through which the cord connection to the variac is led, thus providing a gas-tight seal.

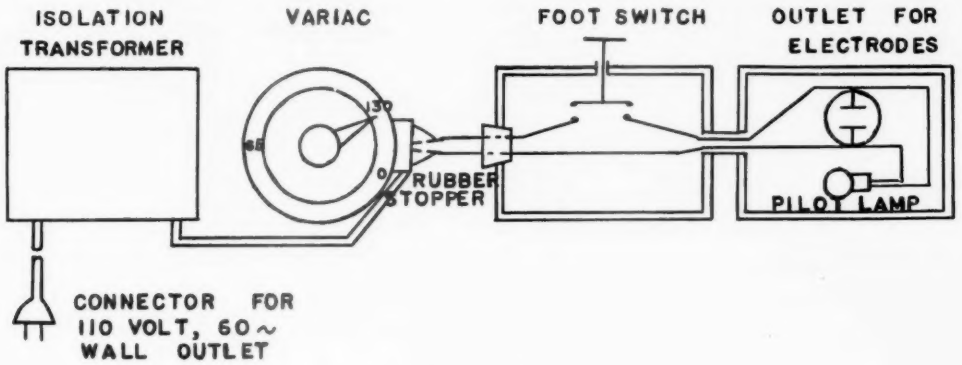

Fig. 2.—Apparatus diagram.

Attached to the foot switch case by means of a pipe nipple is a two-gang condulet. This condulet is fitted with a "Twist-Tite" convenience outlet or receptacle and a 6 watt, 125 volt Mazda pilot lamp. The electric wires are fastened to the convenience outlet and from the outlet to the pilot lamp. The cover on the condulet contains a bull's-eye for viewing the lamp. When the isolation transformer is connected to the power supply and the foot switch is pressed, the pilot lamp lights, indicating that the electrical circuit is alive and therefore working. The "Twist-Tite" outlet takes standard parallel blade caps or plugs. After the cap is inserted, a slight twist will grip it tightly and prevent it from loosening or pulling out. The wiring diagram of the circuit is shown in Fig. 2.

Electrodes.—The electrodes are in pairs and are made of brass rods ¼ inch in diameter, one end of which is bent at a right angle to the axis of the rod. A stainless steel disc .03 inch thick is riveted on the bent end of each electrode (Fig. 3). A number of small holes are drilled about the circumference of each

*General Radio Company, 275 Massachusetts Avenue, Cambridge 39, Mass.

disc to permit the sewing of thick plaster felt to the surface of the discs. At The Johns Hopkins Hospital three pairs of electrodes are available having disc diameters of 1⅛, 1 7/16, and 1¾ inches, respectively. The smallest size electrodes are used for children's hearts, and the others for larger hearts. The largest size possible is used in each case. These electrodes with their cords and plugs are maintained in a sterile condition for use in an emergency.

A small hole, approximately ½ inch deep, is drilled into the ends of the straight portion of the electrode handles and the wires of the cord are soldered into these. In soldering the wires into the ends of the electrode handles, care is taken that the insulation on the wire is flush with the end of the handle.

The brass rods that serve as the electrode handles are insulated by covering them with a ¼ inch inside diameter, 1/16 inch thick wall rubber tubing of the highest grade pure gum stock. A steam-cured nonblooming tubing that will withstand repeated sterilizations without deterioration is used.

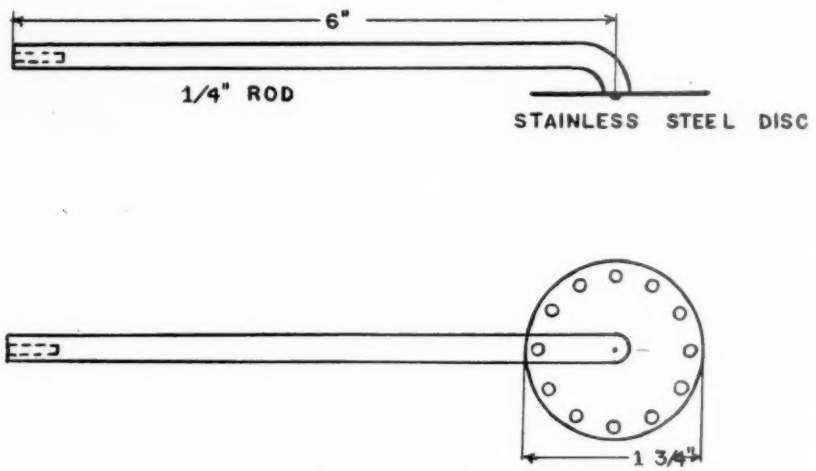

Fig. 3.—Electrodes.

The rubber tubing is cut long enough so that it will cover not only the entire brass handle but will extend about two inches over the insulation of the cord. The rubber tubing is then doubled back on itself so that it serves as a cord protector and prevents the sharp bending of the cord on the handle. Fig. 1 shows a pair of electrodes and illustrates this construction.

The cords used are insulated with neoprene, which is an outgrowth of an aircraft ignition cable insulator developed by the General Electric Company for fighter plane engines. They withstand the heat of sterilization while still retaining the properties of high insulation strength and resistance to moisture, grease, acids, and alkalies. The cords are nine feet in length and are smooth. The plugs are also entirely of neoprene and are a molded integral part of the cord. Each individual wire consists of sixty-five strands and is equivalent to No. 16 B & S gauge. The cords are sold under the trade name of Preen-X heater cords. The cords and plugs were tested for their insulation value and were sterilized fifty times in the autoclave at a potentiometer temperature of

250° to 260° F. for one-half hour. Following the sterilization test, they were checked for appearance and insulation value and found to have suffered no deterioration.

Without doubt there are other cord materials which would be satisfactory. There should, however, be a word of caution as to the plug on the end of the electrode cord which fits into the receptacle. Plugs are often made of composite materials including sealing wax and resins which may soften in the autoclave and melt sufficiently after a number of sterilizations to flow down over the blades of the plug, thus forming a thin film which effectively insulates the blades. Under such conditions no contact is made with the circuit when the plug is pressed into the outlet; therefore, there will not be a current through the electrodes. This possibility has been eliminated by using a solid neoprene plug rather than an ordinary plug.

DISCUSSION

To operate the apparatus, the supply cord to the isolation transformer should be plugged into a 110 to 120 volt: 60 cycle alternating current wall outlet and the variac should be set at 130 volts. The sterilized padded electrodes, with their cord and plug, are connected to the power unit by placing the plug in the convenience outlet next to the pilot light. If the power unit is functioning, the pilot lamp will light when the foot switch is depressed.

In the treatment of ventricular fibrillation it is extremely important to massage the heart prior to an attempt at electrical defibrillation. This was first stressed by Wiggers[6] and its importance later emphasized by Beck and Mautz,[7] who stated that massage must be continued until the heart is no longer dilated or cyanotic before attempting defibrillation. This usually requires one or two minutes.

After the heart has been massaged and is no longer dilated or cyanotic, it is defibrillated. This is accomplished by soaking the felt-padded electrodes in an isotonic saline solution and placing the electrodes on the right side of the right ventricle immediately beneath the right auricular appendage and on the left ventricle at the apex of the heart.

An electric current is then passed through the heart for one second or less by stepping upon the foot switch. If several single shocks fail to defibrillate the heart, it should be massaged for another minute and serial defibrillation, as first described by Wiggers,[8] should be attempted. This consists of passing a series of shocks through the heart. The shocks last ⅓ second and there is a ⅓ second interval between shocks. If a series of six to eight shocks is unsuccessful, the heart should be massaged again and serial defibrillation should be repeated.

Procaine or other myocardial depressants are not usually necessary adjuncts in the treatment of ventricular fibrillation; when they are used, it is more difficult to treat the ventricular standstill that may result following the electrical defibrillation of the heart. If many attempts at serial defibrillation fail,

5 c.c. of 1 per cent procaine may be injected into the left ventricular cavity, the heart massaged for a minute or two, and serial defibrillation again attempted.

Following successful defibrillation, the heart may begin forceful contractions immediately. If it does not, the heart should be massaged for several minutes. If massage alone fails to restore a normal beat, 1/10 to 1/3 c.c. of 1:1,000 epinephrine hydrochloride in 5 c.c. of isotonic saline *or* 2 to 4 c.c. of 10 per cent calcium chloride, as recommended by Kay and Blalock,[9] should be injected into the left ventricular cavity and cardiac massage continued. The cardiac stimulants may be repeated every two to three minutes. It may be necessary to use 1/3 c.c. of 1:1,000 epinephrine hydrochloride before a good beat is restored but it is better to use a smaller dose initially because some hearts may revert to fibrillation with a large dose. It is necessary to continue vigorous cardiac massage about forty times per minute until effective spontaneous cardiac contractions occur.

SUMMARY

A simply constructed, inexpensive apparatus for electrical defibrillation of the heart has been described. With such an apparatus the possibility of successful treatment of ventricular fibrillation arising during surgery is greatly increased.

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THE ANTERIOR CHAMBER OF THE EYE FOR INVESTIGATIVE PURPOSES

A Site for Transplantation of Fetal Endocrine Tissues and Cancer, and for the Study of Tissue Reaction

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THE purpose of this paper is to point out certain uses to which the anterior chamber of the eye is particularly adapted for the investigation of various problems which are not necessarily ophthalmologic. During the past 2 years, in the Surgical Research Laboratory of the Buffalo General Hospital, the anterior chamber of the eye has been used in the study of: (1) tissue reaction to foreign materials; (2) the homologous transplantation of fetal endocrine tissue in adult nonrelated hosts; and (3) the heterologous transplantation of human cancer.

I. The Anterior Chamber of the Eye for the Study of Tissue Reaction to Foreign Material

Since the time of Cohnheim, studies of this nature have used the classical and standard histologic techniques for the study of sterile inflammation. In certain instances, such a laborious and time-consuming procedure is unnecessary if one elects to use the anterior chamber of the eye. By using this method, one may observe the eye daily for tissue reaction. Fig. 1 demonstrates a small piece of polyethelene tubing inserted into the anterior chamber of a rabbit's eye some 3 months previously. This piece of tubing was brought to our laboratory by a member of the department of anesthesia who wished to know if the tubing was reactive. The anesthetist wished to place the tubing within the spinal epidural space in order to give analgesia, over a period of several weeks, to a patient with an inoperable and painful carcinoma. If the anesthetist has at his disposal nonreactive tubing, he may, in selected cases, spare the patient a cordotomy for the relief of intractable pain. One will note from Fig. 1 that as far as tissue reaction is concerned there is little, if any. The piece of tubing may be used with safety, as far as tissue reaction is concerned, over a period of several weeks. The orthopedists are still looking for the perfect nonreactive metal for the plating of bones, the nailing of hips, and so on. It might well be that such a method of observing the tissue reaction to metals would be of value to the orthopedists; it also offers a method of observing the tissue reaction to various suture materials. After the initial reaction to the corneal incision is over, the eye will continue to show signs of progressive

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tissue reaction if the foreign material is reactive but will clear entirely if tissue reaction is minimal. Thus the enormous amount of histologic study which is now necessary for such an investigation may be saved.

Fig. 1.—Rabbit with test sample of polyethylene tubing placed in the anterior chamber of the eye for over 3 months. Demonstrates minimal tissue reaction.

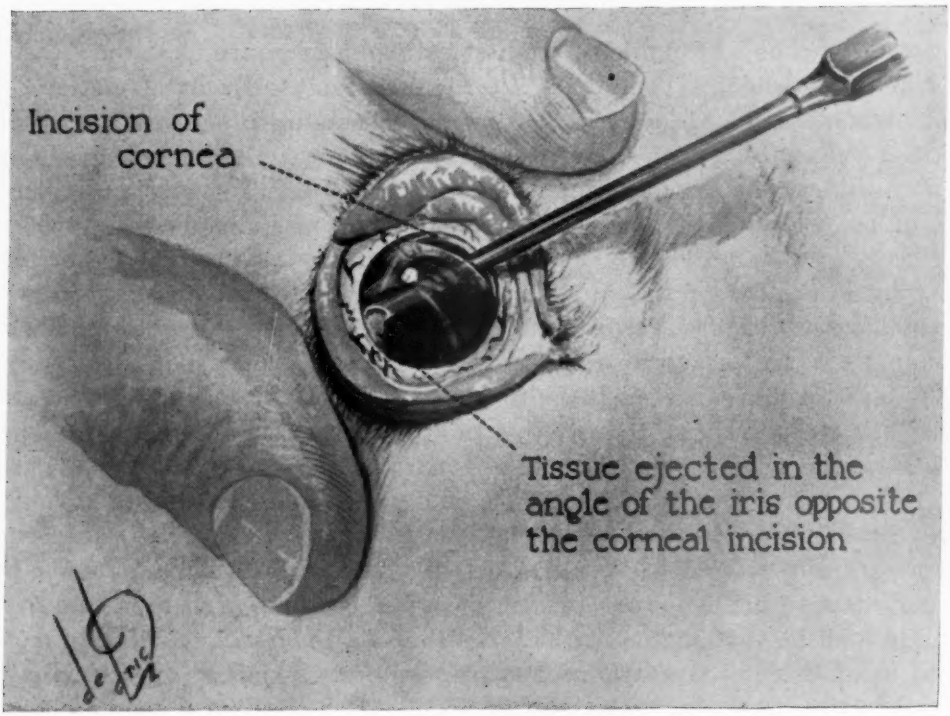

Fig. 2.—Illustration of the method of transplanting fetal endocrine tissue or cancer to the anterior chamber of the eye.

II. HOMOLOGOUS TRANSPLANTATION OF FETAL ENDOCRINE TISSUES TO ADULT NONRELATED HOSTS

Early embryonic tissues have apparently not developed tissue specificity. In other words, fetal tissues possess autonomy and may be transplanted homol-

ogously to the anterior chamber of the eye, with indefinite survival. Fetal transplants of adrenal, ovary, testes, and thyroid tissue have been made in the dog, guinea pig, and rabbit.[1]

Method.—The feti are removed aseptically by cesarean section and, with the aid of a dissecting microscope, the endocrine tissues are removed and placed in a sterile Petri dish. The bottom of the dish contains a few drops of the

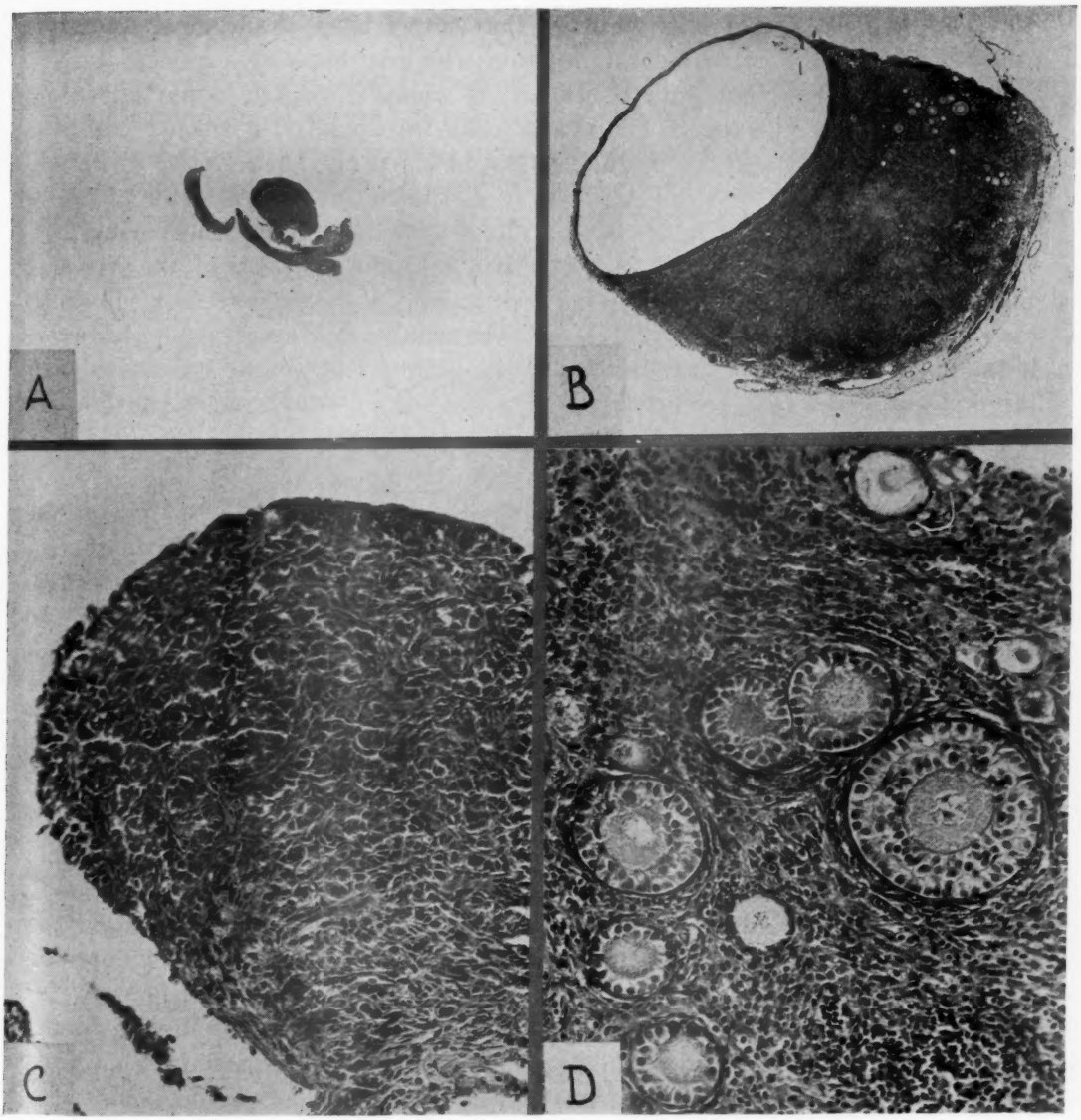

Fig. 3.—*A*, Section of control fetal ovary, approximately twentieth day gestation (hematoxylin and triosin, ×35).

B, Rabbit 80. Identical fetal ovary 66 days after homologous transplantation to the anterior chamber of the eye. Note the increase in size, the development of an ovarian cyst, and the mature follicles (hematoxylin and triosin, ×35).

C, Higher magnification of *A* demonstrating immature fetal development of the ovary (hematoxylin and triosin, ×300).

D, Higher magnification of *B* demonstrating the developing follicles in greater detail (hematoxylin and triosin, ×300).

mother's blood, which will furnish sufficient serum to keep the tissues moist until transplanted. Drying of the tiny tissue fragments, and sepsis, are the 2 greatest deterrents to successful transplantation of endocrine tissues. The endocrine tissues for transplantation are removed between the nineteenth and twenty-second day of gestation in the rabbit and between the thirtieth and forty-second day in the dog and guinea pig.

The eye of the host is anesthetized with either 7 per cent cocaine or 1 per cent pontocaine. Fig. 2 is a drawing that shows a small incision along the upper border of the corneoscleral junction which is made by a quick jab of a corneal knife. Sufficient fluid is allowed to escape in order to partially collapse the anterior chamber. The tissue to be transplanted is placed within a small sterile trochar and the trochar is then inserted into the anterior chamber. The tissue is ejected from the trochar by a stillette into the inferior angle of the iris opposite the corneal incision. The fragment of tissue, measuring 2 to 3 mm. in diameter, is guided farther down into the junction of the iris and conjunctiva by external pressure on the cornea. It is not necessary to close the corneal incision. Postoperative care is usually not necessary. However, if the eye becomes encrusted, this should be removed by simple irrigation with tap water in order to avoid infection. The use of chemotherapy and antibiotics for the control of infection is not necessary, and should not be employed as a substitute for asepsis.

There is always an initial corneal reaction to the stab wound and to the slight trauma which is necessary in guiding the tissue fragment into the inferior angle of the iris. The operative procedure may cause slight hemorrhage. However, within 10 to 15 days the cornea has, as a rule, cleared sufficiently to permit examination of the transplant. By this time the transplant has a pink color which is indicative of survival. When examined with the low power of a stereoscopic microscope, an invasion of the transplant with tiny capillaries may be observed, the invading capillaries being derived from the iris. Between the third and fourth weeks, larger invading vessels may be observed with the naked eye. A transplant which does not survive has a pearl-white appearance resembling thick fibrous tissue. The dead transplant may either be absorbed or remain to become encapsulated and replaced by fibrous tissue. Microscopically the reaction and absorption is a lymphocytic infiltration followed by fibroblastic proliferation and replacement by fibrocytes. Polymorphonuclear leucocytes are seldom observed invading the transplants. No transplant has been recorded as a "take" unless there was histologic evidence of growth and maturation for longer than 30 days. If regression is going to occur, it is usually apparent before 30 days.

Criteria of a "take" are as follows: At the time of transplantation a control fetal gland, from the same litter of feti, is fixed for histologic study, the size and cellular maturity of the fetal endocrine organ being noted. The transplant when removed at a later date is compared with the control section for cellular differentiation into an adult gland and for size. No transplant has been classified as a "take" unless there has been continued growth and cellular

differentiation for 30 days or longer. This arbitrary time limit has been set since Leo Leob found most of his homologous transplants regressed at the end of 3 weeks.[6]

Results.—Transplants have been made in over 230 rabbits, 170 guinea pigs, and 53 dogs. One may obtain a 50 to 60 per cent survival and continuous growth in the homologous embryonic transplants of adrenal, ovary, testes, and thyroid tissue in adult normal guinea pigs and rabbits. In the dog, the anterior chamber is very large, which allows many of the transplants to float to the center of the cornea, where they die because of lack of blood supply. Therefore, the percentage of "takes" is less in the dog. In castrated and thyroidectomized hosts, the percentage of "takes" of the ovaries and testes and the thyroid may be increased from 60 per cent to approximately 90 per cent. This observation indicates that Halsted's Law of Endocrine Deficiency[2] is valid and will be reported in greater detail in another communication.

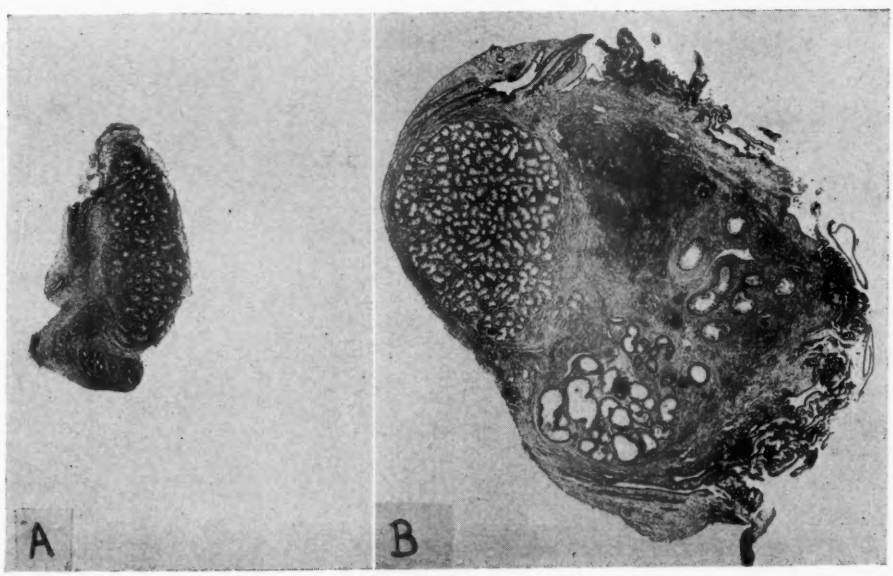

Fig. 4.—*A*, Section of control fetal rabbit testes, twentieth day gestation (hematoxylin and triosin, ×35).
B, Rabbit 77. Identical testes removed 49 days after transplantation (hematoxylin and triosin, ×35).

The transplant which survives will increase its volume 300 to over 1,000 times the original volume. There is cellular maturity and differentiation from the fetal form to the adult form.

Ovaries: The fetal transplants when removed 60 to 180 days after transplantation show mature Graafian follicles (Fig. 3). In the rabbit, the ovarian transplant at this time will yield a positive Friedman test if the animal is injected intravenously with pregnant urine. Cysts are often formed. The histogenesis of these ovarian cysts is under further investigation.

Testes: There is development of all portions of the testes toward an adult form. Spermatids have been observed in the rete testes (Figs. 4 and 5). Spermatozoa have not been observed.

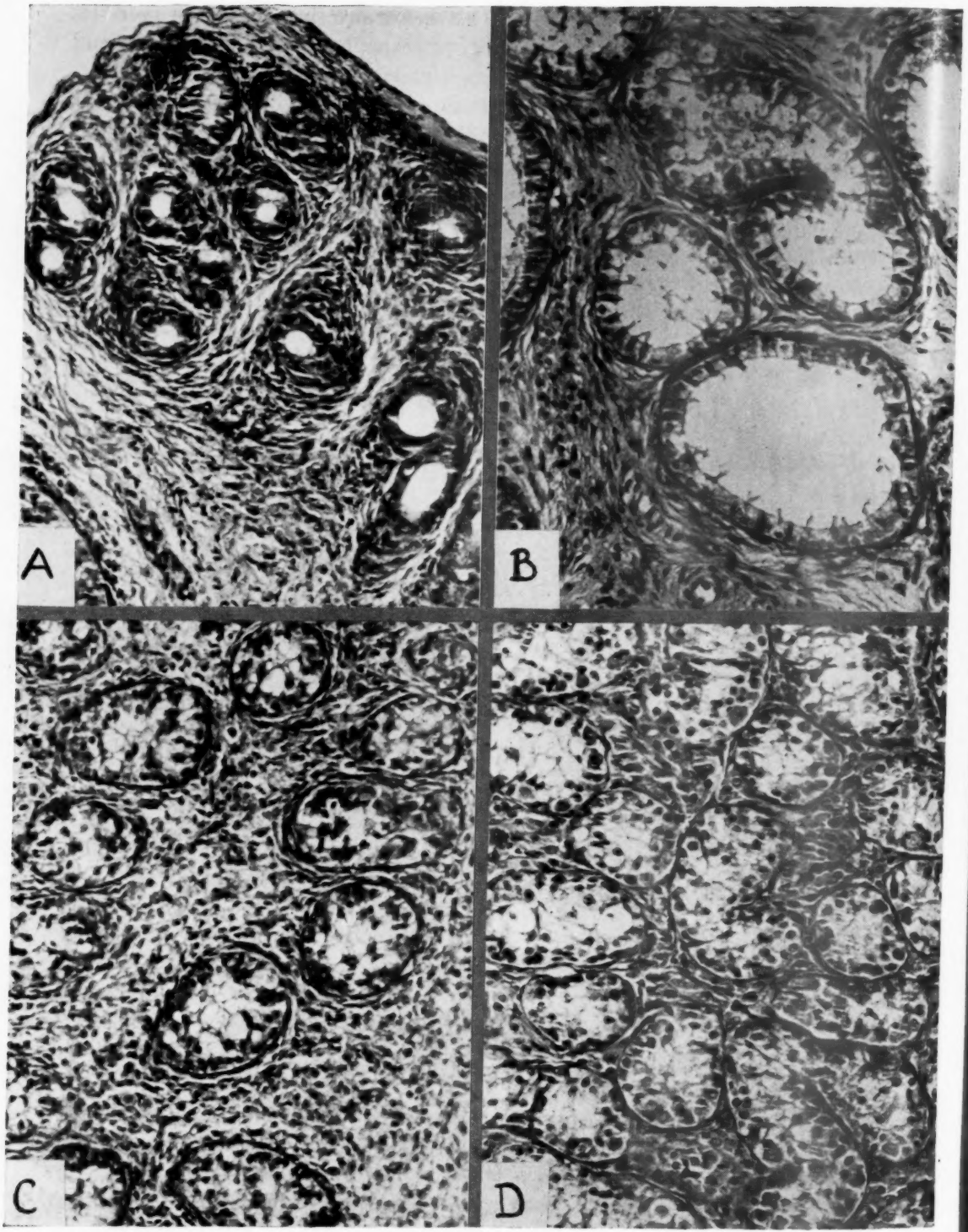

Fig. 5.—*A*, Higher magnification of Fig. 4, *A* to demonstrate the cellular detail of the rete testes in the control section (hematoxylin and triosin, ×300).

B, Higher power magnification of the rete testes of the transplant, Fig. 4, *B*, demonstrating spermatid formation (hematoxylin and triosin, ×300).

C, Higher power magnification of the seminiferous tubules of fetal testes (hematoxylin and triosin, ×300).

D, Same magnification of seminiferous tubules of the transplant demonstrating increased maturation, (hematoxylin and triosin, ×300).

Adrenal: The best growths occur in those hosts who have had a unilateral adrenalectomy; the transplant grows faster and its volume is greater (Fig. 6). There is cellular differentiation into all 3 zones of the adrenal cortex (Fig. 7). The adrenal medulla does not survive.

Thyroid: In the fetal thyroid the follicles are tiny, immature, and rarely possess colloid. The transplant removed 60 days to over 1 year later is fully developed. The follicles are lined with low cuboidal epithelium and there is an abundance of colloid present (Fig. 8). Dr. John B. Hursh, of the Division

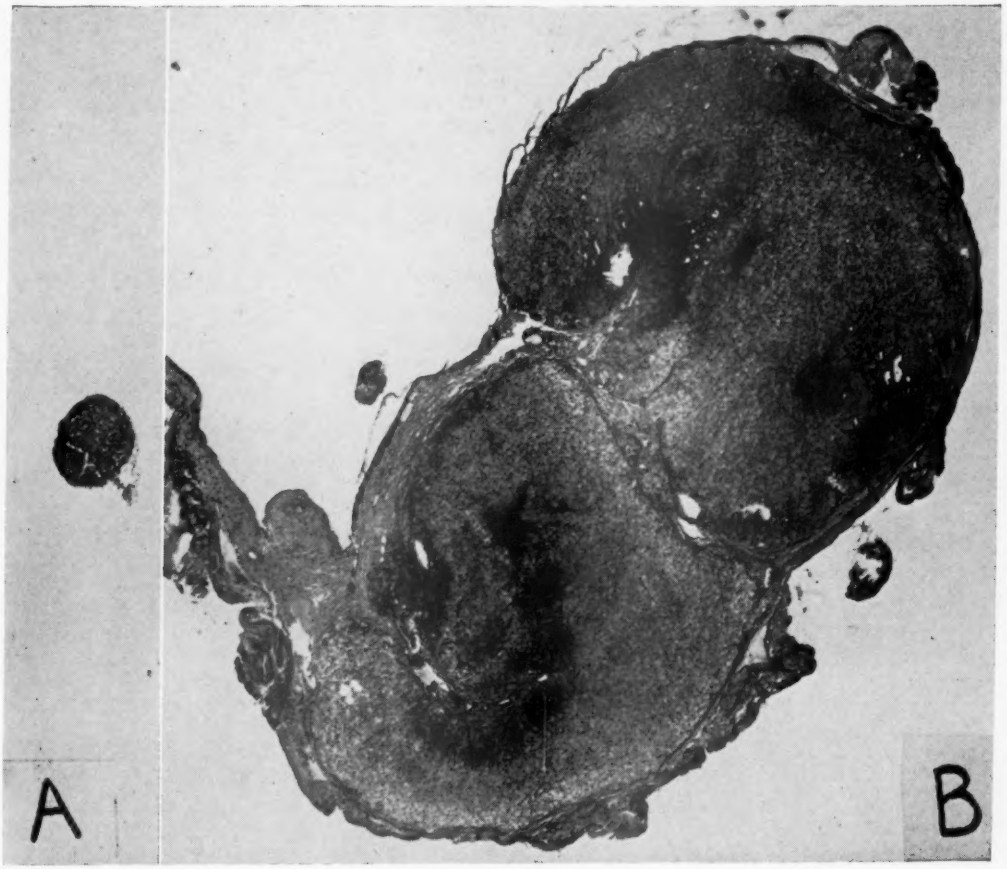

Fig. 6.—*A,* Control fetal rabbit adrenal tissue twentieth day gestation (hematoxylin and triosin, ×30).

B, Transplant removed after 112 days. There has been a volume increase of over 1000 times. The cortex has differentiated into 3 zones (hematoxylin and triosin, ×30).

of Radiology and biophysics of the University of Rochester School of Medicine, gave us invaluable aid in obtaining additional evidence that the thyroid transplant functions. If the animal is injected with radioactive iodine I_{121}, the transplant will take up the iodine to the same degree as the host's normal thyroid tissue. In the thyroidectomized host, the transplant will convert inorganic I_{121} to bound-iodine, indicating that the iodine has been incorporated into the thyroxine molecule. Fig. 9 is an autoradiograph of a thyroid transplant injected with I_{121} 24 hours before the autograph was made. There is

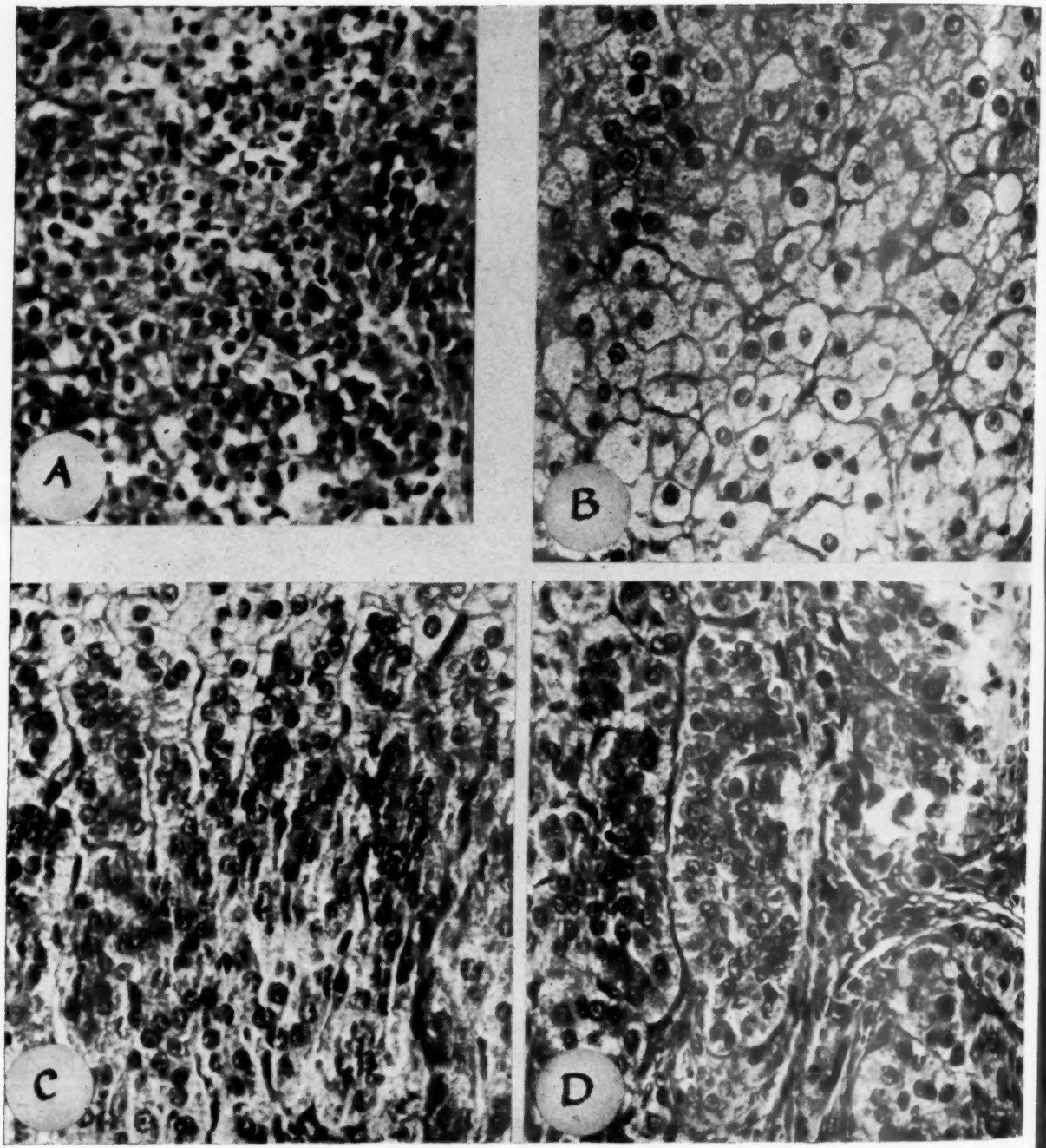

Fig. 7.—Higher power magnification of Fig. 6 (hematoxylin and triosin, ×680).

***A*, Control fetal adrenal tissue demonstrating lack of differentiation and organization.**

***B*, Demonstrating the development of broad, flattened cells of the zona glomerulosa of the transplant.**

***C*, Demonstrating development of the zona fasciculata of the transplant.**

***D*, Demonstrating development of the zona reticularis of the transplant.**

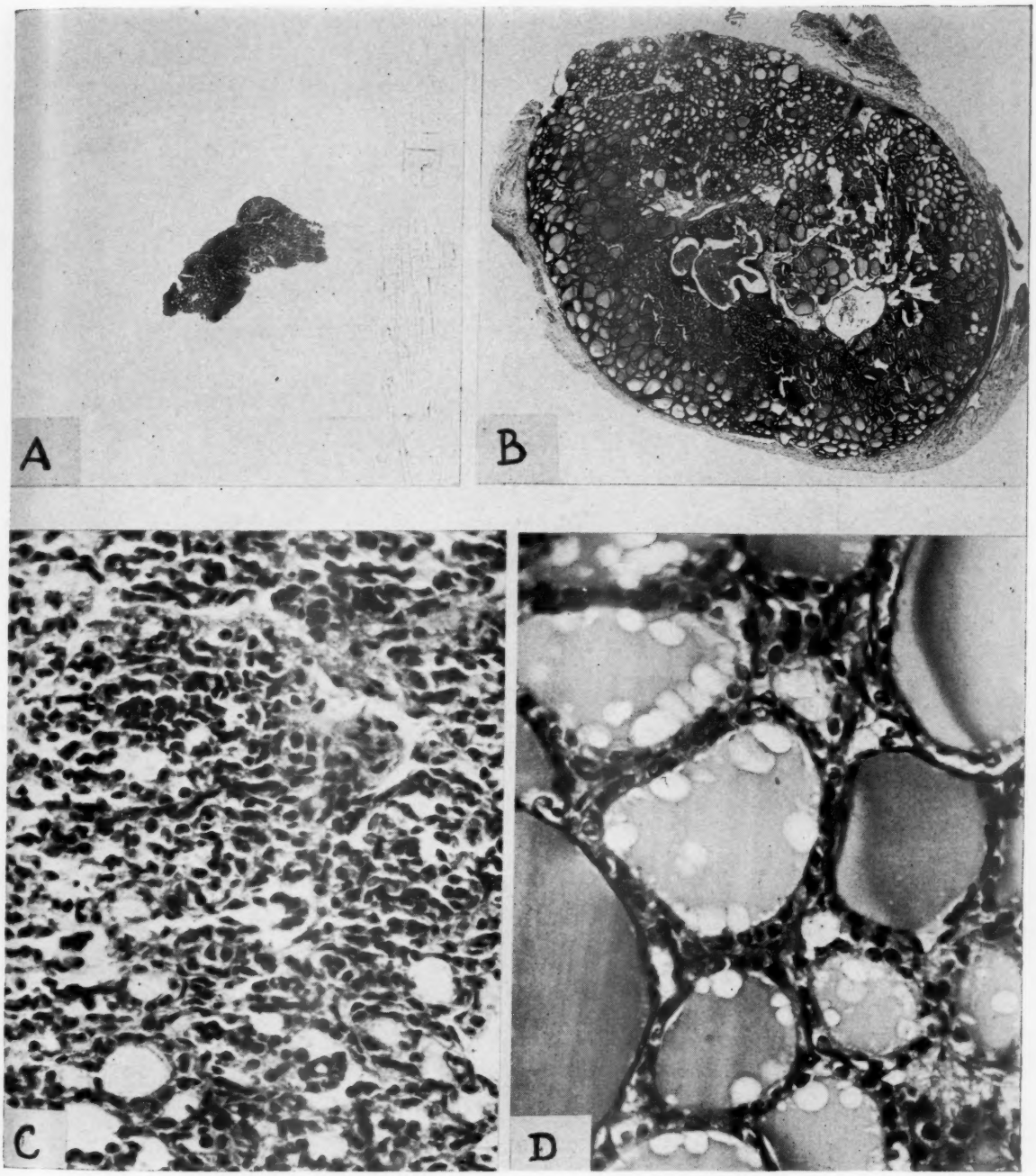

Fig. 8.—*A*, Control fetal rabbit thyroid tissue, twentieth day of gestation (×35).

B, Transplant removed 112 days after transplantation, demonstrating tremendous increase in size and maturation (×35).

C, Higher power magnification of *A* demonstrating the immature follicles and lack of colloid (×680).

D, Higher power magnification of *B* demonstrating mature follicles lined with low cuboidal epithelium and an abundance of colloid (×680).

(Sections stained with hematoxylin and triosin.)

an abundance of radioactive iodine concentrated within the transplant. Fig. 10 is a photograph of a fetal rabbit thyroid transplant which had been growing for over 6 months. In our laboratory, guinea pigs have been kept for over 1 year with transplants. This time represents almost one-half the expected life span of the guinea pig.

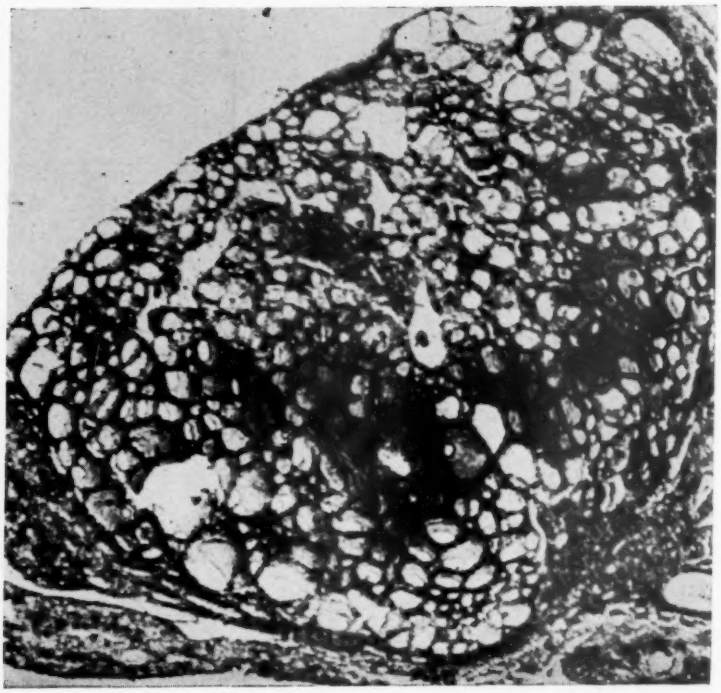

Fig. 9.—Autoradiograph of transplanted fetal rabbit thyroid tissue which had been growing for 112 days, demonstrating the uptake and distribution of radioactive iodine, I_{131}.

Fig. 10.—Fetal thyroid transplant growing in the eye of a rabbit for over 6 months.

Fig. 11.—*A*, Transplant of a human papillary medullary thyroid carcinoma to the anterior chamber of a guinea pig eye (×40). *B*, Higher power of *A* to show the malignant cells (×1,200). *C*, Transplant of a human malignant melanoma to the anterior chamber of a rabbit's eye (×250). *D*, Higher power of *C* to demonstrate the melanotic cells (×1,100). (Sections stained with hematoxylin and triosin.)

These observations indicate that fetal endocrine transplants of adrenal, ovary, testes, and thyroid tissue grow, differentiate from fetal to adult form, and function within the host. Other sites for transplantation besides the anterior chamber of the eye are being investigated in our laboratory in order to obtain a method of transplanting endocrine tissues clinically to deficient patients.

III. TRANSPLANTATION OF HUMAN MALIGNANT TISSUES

Greene[3, 4] has demonstrated on numerous occasions that human cancer may be heterologously transplanted. The ability to transplant human cancer to laboratory animals by Greene's method offers the investigator, for the first time, a method of studying human cancer in living laboratory animals. He has introduced a biologic concept to differentiate the malignant from nonmalignant tissues as contrasted against a purely morphologic classification.[5] For example, the lymphomas and blood dyscrasias do not grow when transplanted to animals. Neither do all tumors which are classified on a morphologic basis as being cancer grow when transplanted to animals. This has led Greene to question such tumors as being true cancers. The purpose of this paper is not to go into a lengthy discussion of the merits of the microscope versus the laboratory animal in the differentiation of cancer, but to re-emphasize the fact that human cancer may be studied in laboratory animals. For example, the susceptibility of human malignant tissue to drugs, hormones, or radiation therapy may be advantageously studied in such a manner. Fig. 11, *A* and *C*, is an example of 2 human cancers which have been transplanted to the guinea pig and rabbit in our laboratory.

The thyroid carcinoma was obtained* at the time of a lymph node dissection of the neck. A piece of the cancer was obtained and transplanted to the guinea pig. The cancer grew in the anterior chamber of the eye and was histologically identical to that obtained from the patient. The literature does not reveal a carcinoma of the thyroid as having been transplanted previously.

The malignant melanoma was obtained† at the time of operation and was transplanted within 2 hours to the anterior chamber of the rabbit's eye. The tumor grew and was histologically identical to the original tumor.

SUMMARY

The anterior chamber of the eye is particularly adapted for carrying out many investigative processes.

1. A simple method of studying the tissue reaction to foreign bodies has been demonstrated. This method does not require histologic techniques. The reaction of the tissues to the foreign body may be observed continuously.

2. Early embryonic endocrine tissues, adrenal, ovary, testes, and thyroid, may be transplanted to adult nonrelated hosts. The transplants continue to grow, differentiate, function, and mature into adult glands. From the evidence presented, transplants are believed to function.

*From a patient of Dr. Roswell Brown.
†From a patient of Dr. Winfield Butsch.

3. The advantages of using the anterior chamber of the eye for the transplantation, biologic differentiation of malignant and nonmalignant tissues, and as a method for the study of human cancer has been emphasized. The successful transplantation of a human thyroid cancer to the guinea pig and the transplantation of a human malignant melanoma have been presented.

Acknowledgments.—The author expresses appreciation to Dr. John R. Paine, Chairman of the Department of Surgery of the University of Buffalo School of Medicine, for his guidance in this investigative work; to Mr. M. D. Dedrick, of the Department of Medical Illustration, for the illustration and assistance in making the photomicrographs; and to Miss Marjorie W. Egan, for technical assistance.

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THE CLINICAL PHYSIOLOGY OF THE HUMAN BRONCHI

II. The Effect of Vagus Section Upon Pain of Tracheobronchial Origin

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IN A PREVIOUS communication[1] clinical evidence was presented concerning the referral of pain of tracheobronchial origin. This was demonstrated by electric stimulation of the mucosa of the bronchial tree during bronchoscopy. The anterior chest and cervical areas to which the pain was referred were charted. In general, stimulation of the posterior wall of the main bronchi resulted in pain referred to the homolateral anterior chest wall within 4 cm. of the sternum or to the anterior cervical region within 2 cm. of the midline. Stimulation of the posterior wall of the trachea resulted in referral to the anterior midline at points extending from the larynx to the xiphoid. No explanation was offered concerning which nervous pathways transmitted these impulses to the central nervous system. Further studies have since been made and are presented in this report. These permit certain conclusions to be drawn concerning the afferent innervation of the tracheobronchial tree. A review of the pertinent literature concerning the afferent innervation of the lungs and respiratory tree follows.

The nerve supply to the tracheobronchial tree arises from both the sympathetic and parasympathetic systems, or together from the autonomic system. This furnishes efferent motor as well as secretory fibers. Both the vagus and sympathetic systems contain afferent fibers which are not part of the autonomic system.

An extensive amount of experimental work has concerned the visceral afferents reaching the central nervous system by way of the vagus. In 1868 Hering and Breuer[2] presented evidence that afferent fibers carrying sensory impulses from the lungs and respiratory tree were included in the vagus nerve. Möllgaard,[3] in 1912, later confirmed by Molhant,[4] accomplished the classic tracing of the afferent nervous pathways from the lungs and respiratory tree. Following pneumonectomy in animals, and after allowing sufficient time for nerve degeneration, he noted the presence or absence of degenerative changes in the cells of the nodose ganglia, the cervical ganglia, and dorsal nucleus of the vagus, as well as in the vagal trunk. He concluded that the nodose ganglia contain nerve cells which are analogous to the cells of the posterior nerve root ganglia of the spinal cord, and that their dendrites subserved the transmission of afferent impulses from the lung.

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Dixon and Ranson[5] demonstrated the presence of afferent fibers in the vagal trunk of the cat by stimulating the proximal end of the transected vagus, thereby producing bronchodilatation when both vagal trunks had been cut. Inasmuch as the reflex was only abolished by transection of the cervical spinal cord at any level distal to the entrance of the vagal fibers, it was concluded that the reflex pathway traversed the vagal afferents to the medulla, passed from the medulla through the lateral columns of the cervical cord, and then was carried in the sympathetic chain through the first, second, and third thoracic white rami to the stellate ganglion and on through the accelerator nerve to the bronchi. It was implied, but not specified, that vagal section was performed in the cervical region.

A series of experiments involving the production of a respiratory reflex by chemical or mechanical stimulation of the deeper respiratory passages, performed in animals from 1900 through 1924, demonstrated the presence of afferent nerve endings within the tracheobronchial mucosa.[6-10] In some instances bilateral vagus section abolished this respiratory reflex, giving rise to the conclusion that the afferent endings were connected with nerve fibers which pass through the vagus nerves to the medulla.[6-8] However, Roger[9] and Craigie,[10] repeating the same experiments, found the respiratory reflex to be unaffected by section of both vagal trunks (level of section not specified), or by section of the pulmonary branches of the vagus, and they postulated that the afferent impulses traveled through the thoracic sympathetics to the spinal cord and then to the medulla oblongata.

In 1921 Ranson[11] stated that the vagus supplies afferent fibers to the larynx, trachea, and lungs, the cells of origin being in the nodose ganglia. The central fibers run to the nucleus of the tractus solitarius. From cells in the nucleus solitarius fibers arise which ascend and descend in the reticular formation of the brain stem and make connection with the various visceral motor nuclei. This gives rise to the following reflex arc: (1) primary afferent neurone of the vagus; (2) secondary afferent neurone with its cell body in the nucleus of the tractus solitarius; (3) visceral efferent neurone with its cell of origin in one of the nuclei of the visceral efferent column.

Ranson assumed that the afferent fibers of the vagus proceeding from the end organs within the lungs were of two kinds, inspiratory and expiratory, and that each exerted its dominant influence over the rhythm of the respiratory center.

Using histologic methods, Larsell[12] made a thorough investigation of pulmonary innervation in the rabbit. Three types of afferent endings were described. Moreover, the observed difference in histologic structure, correlated with the anatomic position, suggested three functional types of sensory nerve endings: (1) bulbous nodules in the trachea and larger bronchi responding to tactile stimulation, (2) thickened epithelial nodules in the bronchioles responding to tactile and collapse stimulation, and (3) thinly encapsulated terminals in the atria, responding to distention and possibly to chemical stimuli. His later work[13] traced the afferent and efferent pathways

from the nerve endings in the lungs and respiratory tree after midcervical section of the vagus. After unilateral midcervical vagotomy, and after allowing time for nerve cell degeneration, a few sensory terminations remained in the lung of the operated side; however, these were believed to be derived, in part, from the contralateral vagus. Studies on man performed at a later date revealed no histologic differences from his earlier findings.[14]

Heinbecker and O'Leary,[15] experimenting with cats, stimulated the central end of the vagus, transected just below the recurrent laryngeal nerve, after the animal had recovered from the anesthesia required for the preparation. The reaction was similar to that produced by painful stimuli. However, they concluded that there was a scarcity of pain fibers in the vagus as compared to the splanchnic and saphenous nerves, inasmuch as a greater stimulation of the vagus was required to arouse pain than of the other nerves.

Working with a more refined technique, using the cathode-ray oscillograph, Adrian[16] was able to isolate fasciculi of two to four afferent fibers within the vagus of the cat. Limiting his researches to those end organs responding to lung movement, pressure, and distention, he measured the passage of nerve impulses by determination of changes in electric potential, thus confirming the existence of the Hering-Breuer reflex. During inspiration these impulses increased in frequency, traveling from the atria on up to the respiratory center with a resultant stimulation of the next expiration. When the lungs were deflated more than usual with normal expiration, a second set of impulses was transmitted along the vagus, resulting in initiation of the next inspiration.

Histologic studies of transverse sections of the vagus trunk in the cat, subsequent to transection of the vagal roots with allowance of sufficient time for degeneration, revealed that only 20 to 35 per cent of the nerve fibers had degenerated. Therefore, Foley and Du Bois[17] assumed the vagus to be predominantly a sensory nerve. However, in an attempt to correlate their findings with the numerous well-known motor functions of the vagus, they stated that the vagus still had a higher number of motor fibers, as compared to sensory fibers, than the ventral branch of the seventh cervical root, or any one of the ventral roots of the thoracic, lumbar, coccygeal, or sacral nerves of the cat. They also postulated that one preganglionic vagal fiber may synapse with twenty to thirty postganglionic fibers, as has been demonstrated in the sympathetic system. This would allow a greater diffusion of motor activity to take place than would seem apparent from the actual anatomic number of motor fibers as compared to sensory fibers.

White and Smithwick,[18] in their table of visceral pain, stated that, although the lung parenchyma is insensitive, pain from the larger bronchi is transmitted over somatic vagal axones.

Less work has been done on the sympathetic component of visceral afferent innervation of the lungs and tracheobronchial tree. Head,[19] in a study of the distribution of sensory fibers from the spinal nerves through the sym-

pathetic system, based on a comparison of the areas of referred pain in visceral disease, concluded that sensory fibers from the lungs terminated in segments T 1, 2, 3, 4, and 5.

Tracing the nerve pathways by studies of nerve degeneration following pneumonectomy in animals, Möllgaard[3] established the existence of efferent pathways from the spinal cord through the white rami communicants to the stellate ganglion where there is a cell station. He found centripetal fibers (afferent) passing to the second and third thoracic spinal ganglia. From this he deduced the possibility that the spinal cord may transmit certain pulmonary reflexes.

The physiologic experiments of Barry[20] and Molhant[4] clearly demonstrated that afferent impulses from the lung travel through the sympathetic trunk and white rami communicants to reach the spinal cord.

Dixon and Ranson,[5] by measuring the volume of the right middle lobe placed in an oncometer, concluded that stimulation of the upper thoracic sympathetic trunk produced bronchodilatation. The sympathetic efferent pathway was thought to travel from the cord through the upper three thoracic white rami communicants to the stellate ganglion, where a synapse with postganglionic fibers was made to form the final common pathway to the bronchi through the accelerator nerve. Although the physiologic reflexes produced by stimulation of the proximal end of the transected thoracic sympathetic trunk were variable, they provided evidence for the presence of visceral afferent fibers traveling to the cord via the sympathetic trunk from the lungs and respiratory tree.

Histologic studies in the cat revealed large sensory fibers from the upper three thoracic white rami and a few fibers from the fourth and fifth thoracic white rami which could be traced upward through the sympathetic trunk and stellate ganglion to be distributed to the heart and lungs.[11]

Jackson[21] stated that pain is rarely noted during bronchoscopic examination and that real pain is extremely rare when a foreign body lodges in the tracheobronchial tree; nevertheless, he also stated that pain arising from the bronchi and lungs is most commonly felt as segmental pain in the third, fourth, and fifth cervical dermatomes and is probably transmitted to the central nervous system by way of sympathetic afferent fibers through the white rami communicans to the cord.

Thus, other than from deductions dependent upon clinical experience, our knowledge concerning the visceral afferent innervation of the lung and respiratory tree is based almost solely upon animal experimentation. It is for this reason that we present the following experimental study made in our bronchoscopic clinic.

CLINICAL INVESTIGATION

In our clinic, transection of a vagal trunk just below the origin of the recurrent laryngeal nerve, but above the pulmonary plexus, has been practiced in a number of patients with advanced bronchogenic carcinoma, found to be

inoperable at exploratory thoracotomy. This was done in an attempt to relieve their pain and often severe cough. In eight of these patients, subsequent to their recovery we again stimulated the tracheobronchial mucosa by an induced current during bronchoscopy, using the procedure which we have previously presented.[1] In contrast to our previous studies made on patients with both vagal trunks intact[1] (Fig. 1) no pain was noted over the homolateral

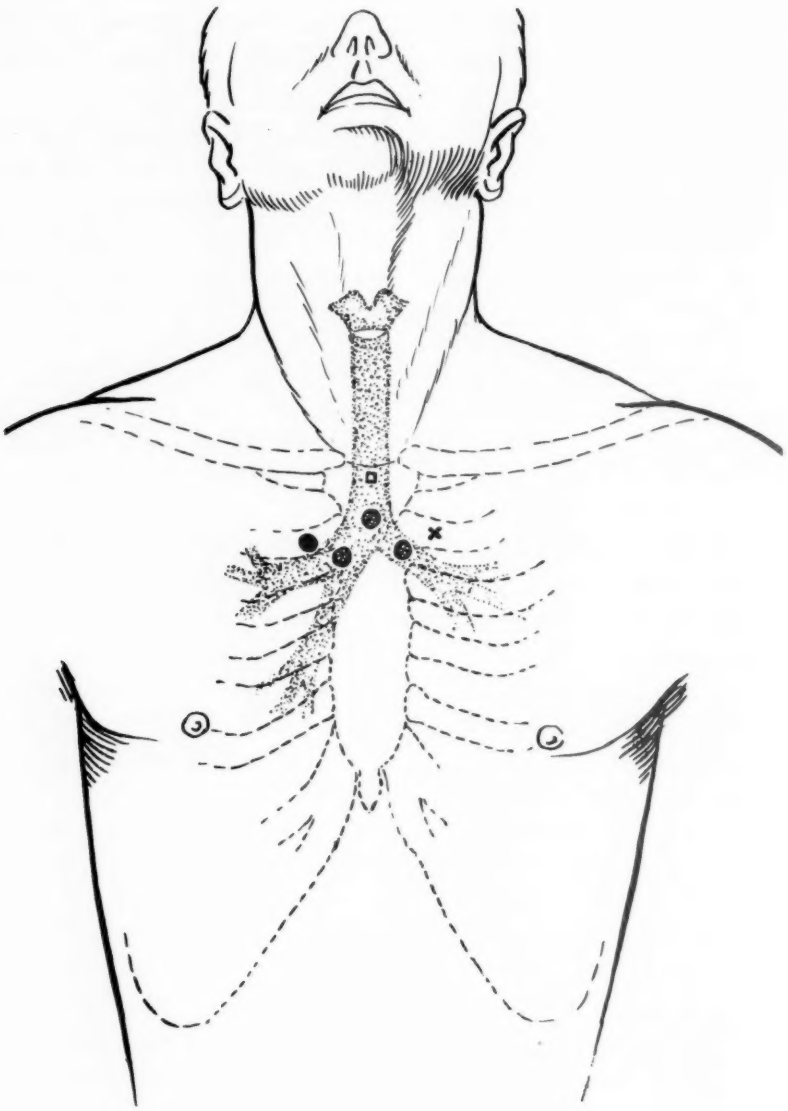

Fig. 1.—Diagrammatic representation of the typical localization of pain subsequent to electric stimulation of the tracheobronchial tree in a patient with both vagus nerves intact. In all patients the tracheobronchial tree was stimulated at three constant sites, represented by the crosshatched circles; the posterior wall of the right main bronchus, the posterior wall of the left main bronchus, and the posterior wall of the trachea 1 cm. proximal to the carina. The solid circle represents the localization of pain in the anterior chest wall produced by stimulation of the right main bronchus; the square, pain from the trachea; and the cross, pain from the left main bronchus. This key is also employed in Figs. 2 and 3.

chest or neck subsequent to stimulation of the main bronchus on the side of the transected vagus. However, in three of the eight patients, electric stimulation of the main bronchus on the side of the previous vagotomy resulted in pain which was noted in the contralateral anterior cervical region. Stimulation of the posterior wall of the trachea 1 cm. proximal to the carina usually referred pain to the midline of the anterior chest or neck, as in patients with both vagal trunks intact, but was absent in one instance (Figs. 2 and 3).

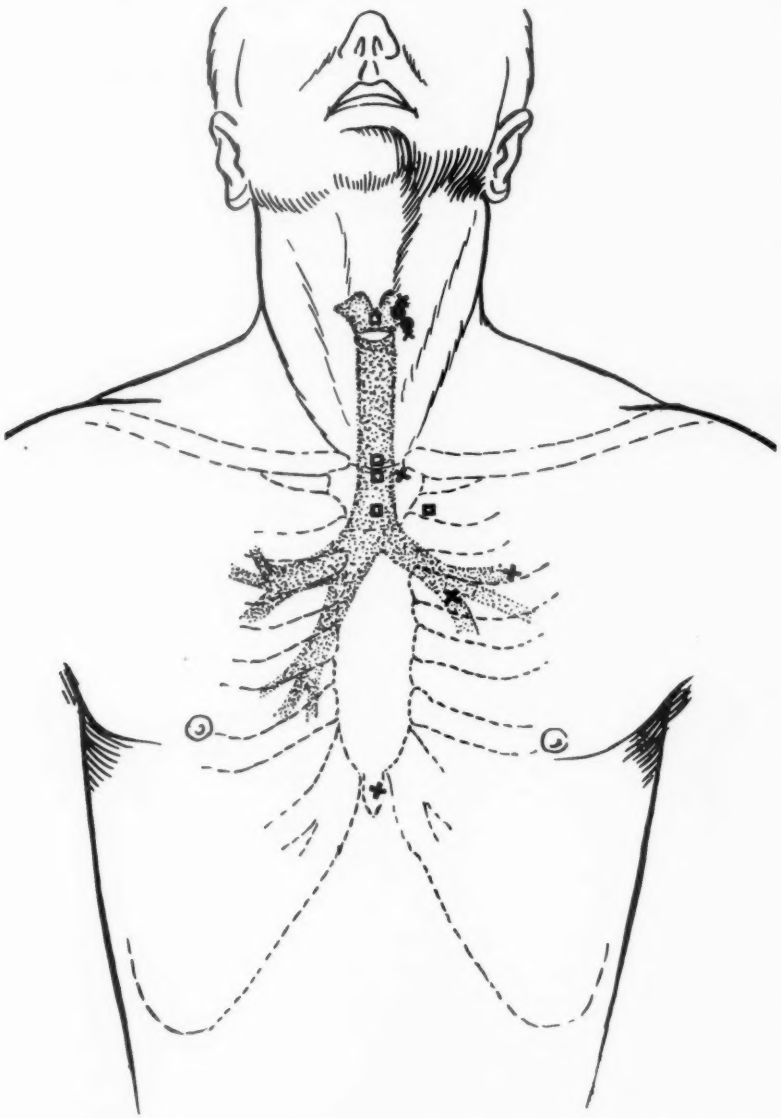

Fig. 2.—Diagrammatic representation of the localization of pain in the anterior chest and cervical regions produced by electric stimulation of the tracheobronchial tree in six patients following transection of the right vagus nerve immediately below the origin of the recurrent laryngeal nerve. The identical three sites as indicated by the crosshatched circles in Fig. 1 were stimulated in these patients. Note the absence of pain in the homolateral chest. In two of the patients in whom the right vagus nerve was transected, electric stimulation of the posterior wall of the homolateral main bronchus resulted in pain which was referred to the contralateral anterior cervical region as represented by the two solid circles.

These findings indicate that in man the afferent fibers which transmit pain impulses from the main bronchi are usually carried by the homolateral vagus. The best explanation for the occurrence of pain on the contralateral side of the vagotomy upon stimulation in the above three patients is the existence of a partial crossing of afferent fibers from the contralateral vagus. These conclusions in the human being confirm the histologic findings of Larsell[12, 13] in the experimental animal.

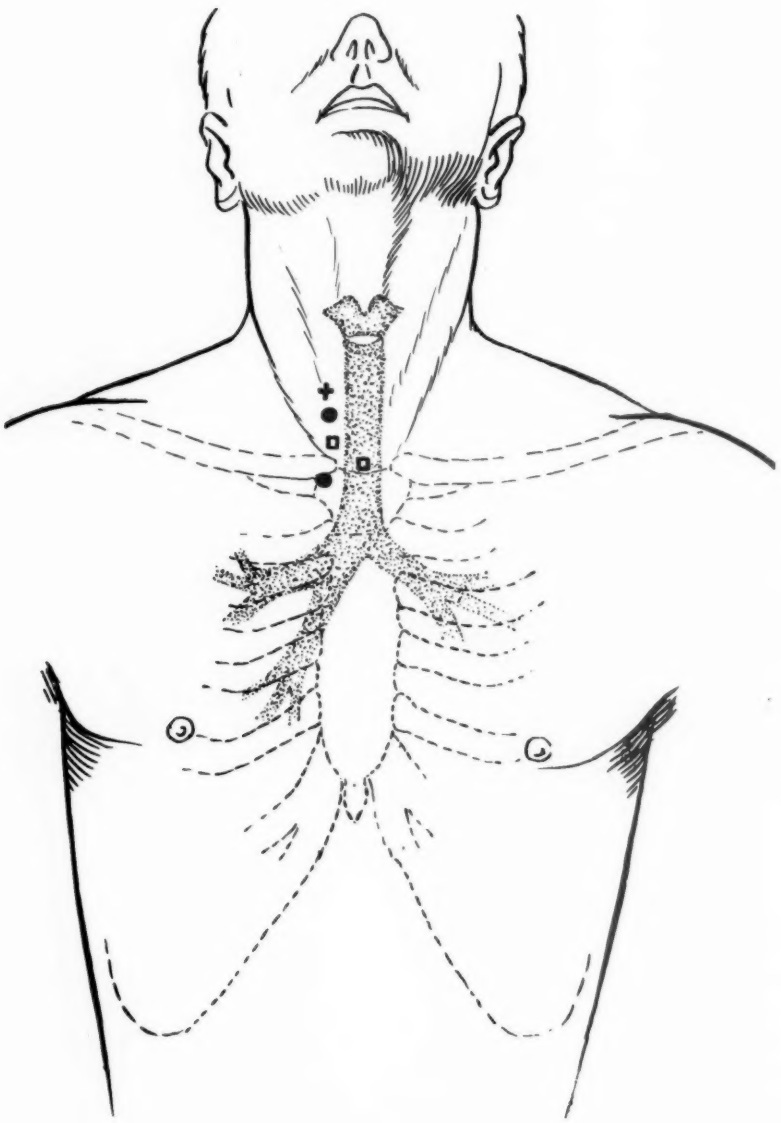

Fig. 3.—This diagram, utilizing the same technique, represents the localization of pain in two patients following transection of the left vagus nerve immediately below the origin of the recurrent laryngeal nerve. Note the absence of pain in the homolateral chest. In one patient, electric stimulation of the homolateral left bronchus resulted in pain which was referred to the contralateral anterior cervical region as represented by the cross.

DISCUSSION

In order to understand the nervous pathways involved in the transmission of pain from the tracheobronchial tree, together with the mechanism of referral, four possibilities should be considered:

1. The pain felt over the anterior chest may represent true visceral pain: that is, pain localized within the wall of the bronchi. However, this would not explain those instances in which the pain is felt in the anterior neck.

2. Animal experimentation has demonstrated that certain visceral afferent fibers arising from the lungs and respiratory tree reach the spinal cord by way of the sympathetic trunk. Patients complaining of pain of cardiac origin are often relieved by surgical procedures interrupting the sympathetic afferent supply of this organ. Considering the anatomic proximity of the heart to the hilus of the lungs, we might postulate that pain of tracheobronchial origin is transmitted over a similar sympathetic pathway; however, this is most unlikely, inasmuch as pain of tracheobronchial origin was abolished on the homolateral side following unilateral vagus section in the majority of our patients.

3. Mackenzie's theory[22] of the mechanism of referred pain affords an explanation for the referral of pain originating in the tracheobronchial tree to the anterior cervical region. On the basis of Larsell's work, Rasmussen[23] postulated the probable nerve pathways underlying the reflexes and referred sensations associated with pathologic involvement of the lung. He stated that reflexes from the lungs are carried to the central nervous system by two routes: (1) the vagus, which carries the visceral afferent fibers from the lung parenchyma and respiratory tree, and (2) the upper thoracic spinal nerves which innervate restricted regions of the pulmonary pleura. In the absence of pleural involvement he considered the vagus to be the chief nerve transmitting these reflexes and referred sensations. His explanation for the referral of pain to the cervical regions in cases of pulmonary pathology is based in part upon the anatomic work of Cajal and Freeman. The latter investigators demonstrated that the sensory fibers of the vagus enter the upper portion of medulla oblongata, where some terminate in the immediate neighborhood, while others run downward toward the spinal cord as part of the tractus solitarius, and a few fibers may even go down to the fourth or third cervical segment. Rasmussen then postulated that an abnormal number of impulses transmitted to the gray matter of the midcervical segments of the cord, as a result of inflammation or other irritating conditions in the lung, would probably account for the referred pain located in the cutaneous areas supplied by the midcervical nerves.

4. The best explanation of the localization of pain subsequent to electric stimulation of the tracheobronchial tree, is we believe, based upon the following premise. Just as stimulation of somatic nerves may result in pain referred to distant sites, so may stimulation of visceral afferent nerves produce pain in a similar manner. A classical illustration of the former is demonstrated by stimulation of the phrenic nerve (central diaphragm), with its well-known referral of pain to the shoulder. As an example of the latter we offer the following hypothesis based on the clinical investigation reported in this paper.

According to existing knowledge the vagus nerve arises in the medulla from the nucleus ambiguus, the dorsal motor nucleus, and the fasciculus solitarius, the latter being the central terminus for afferent fibers of the pharynx, larynx, and the tracheobronchial tree. It is conceivable that stimulation of the vagal afferents within the tracheobronchial tree may set up an irritation in the area of the fasciculus solitarius, which upon reaching the higher centers of the brain might be interpreted as pain of tracheobronchial origin, or as pain of laryngeal origin.

SUMMARY

1. A review of the literature pertaining to the nerve supply of the lungs and tracheobronchial tree is presented.

2. Unilateral vagus section just below the recurrent laryngeal nerve but above the pulmonary plexus as performed in a series of patients with inoperable bronchogenic carcinoma usually abolished pain of bronchial origin on the homolateral side. In three patients, subsequent to unilateral vagus section, electric stimulation of the homolateral main bronchus referred pain to the contralateral anterior cervical region.

3. The foregoing suggests that the afferent fibers which transmit pain from the bronchial tree are carried by the homolateral vagus nerve. The three instances in which pain was referred to the contralateral anterior cervical region support the theory that the afferent fibers to the tracheobronchial tree may be derived in part from the contralateral vagus.

4. The nervous pathways over which tracheobronchial pain impulses are transmitted to the central nervous system and the mechanism of the subsequent referred pain are discussed.

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THE BRONCHIAL ARTERIES

I. Experimental Occlusion

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OF THE two circulatory systems serving the lung, the pulmonary vascular system has been studied extensively. The bronchial vascular system has been studied morphologically, but few investigations of its role in the nutrition of normal pulmonary tissues have been carried out. Since the time of Reisseissen[58] it has been assumed that the bronchial arterial circulation supplies oxygen and nutrition to the pulmonary parenchyma and the bronchial wall. This concept has led many to the belief that interference with the bronchial arterial blood flow will lead to serious pulmonary changes.[1-4, 12, 13, 18, 38, 53, 60, 77] De Burgh Daly[13] stated that practically all of the tissues of the lung controlling intrinsic pulmonary mechanisms depend on the bronchial vascular system for nutrition and oxygen supply. Any deficiency in this system, he added, might lead to changes in the functional activity of these important intrapulmonary structures. Miller[53] has stated that obstruction of the bronchial artery will lead to infarction and gangrene of the lung. One investigator and co-workers[1-4] have suggested that impairment of bronchial arterial blood flow is the cause of bronchiectasis. The present investigation was undertaken in an attempt to determine the role of the bronchial arterial circulation in the normal dog's lung.

HISTORICAL CONSIDERATIONS

According to Hyrtl,[31] Galen was aware of the existence in animals of aortic branches to the lung; the existence of these vessels was denied by Columbus in 1559 but they were again described by Marchettis in 1656; and Ruysch in 1721 claimed the discovery of the bronchial arteries although it is apparent that they were known and described previously.

Accurate anatomic studies of the origin of the bronchial arteries in man have been made.[14, 29, 55] The most recent and accurate study is that of Cauldwell and co-workers.[14] The variable origin of the bronchial arteries in the dog has been stressed.[7, 10, 28, 36, 40, 45, 67] Bruner and Schmidt[10] found that in 60 per cent of seventy-five dissections the right posterior bronchial artery, a branch of the fifth or sixth right intercostal artery, was the chief bronchial artery present. Liebow and co-workers[40] found in a small series of dogs that the main bronchial arterial supply for both lungs was derived from right intercostal vessels. Berry, Brailsford, and de Burgh Daly,[7] on the other hand, encountered left bronchial arteries that were derived from a left intercostal artery or from the aorta itself.

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The intrapulmonary distribution of the bronchial artery to the bronchial tree,[31, 34, 36, 42, 46-48, 51-54, 58, 61, 65, 69, 70] pulmonary nerves and ganglia,[5, 7, 58, 70] pulmonary arteries and veins,[5, 7, 28, 34, 46, 48, 57, 69] lymph nodes and lymphoid tissue,[57, 58, 61, 74] and visceral pleura and intralobular septa[36, 47, 49, 50, 58, 78, 79] has been extensively studied in man and animals. The distribution in the dog is strikingly similar to that in man though it has been pointed out that in the dog the pleura receives blood only from the pulmonary artery.

Miller's[46-48, 51-54] work on the intrinsic anatomy of the bronchial arterial circulation in man, in the dog, and in other species is classic, and as certain features of this work concern us here a short summary follows. Bronchial arterial blood is returned to the heart in two ways: by bronchial veins and pulmonary veins. True bronchial veins are found only in the hilum of the lung and arise from the first one or two dividing points of the bronchial tree. These bronchial veins empty into the azygos, the hemiazygos, or one of the intercostal veins from whence the blood is returned to the right atrium. From within the lung, bronchial arterial blood is returned to the left atrium by the pulmonary veins either through venous radicles having their origin from the outer venous plexus in the bronchial walls at places where the bronchi divide, from the distal end of the alveolar ducts, or occasionally from other portions of the bronchial tree. Fig. 1 demonstrates diagrammatically the intricacies of this circulation.

Whether or not precapillary anastomoses exist between pulmonary and bronchial arterial systems was a point of dispute among the early anatomists.[16, 17, 25, 30, 35, 36, 41, 58, 59, 73, 79] In the normal dog such anastomoses have not been encountered.[7, 28, 30, 46, 48] Recent work on man, however, by Verloop[69] confirms the impression of other more recent anatomists[9, 34] that such anastomoses do indeed exist. There is ample evidence for the existence of a capillary anastomosis between these two systems,[26, 31, 33, 46, 48, 65] and physiologic studies on the relation of the two systems indicate that a true functional anastomosis exists.[6, 21]

Although the role of the bronchial arterial circulation in the normal lung is not well known, there is considerable evidence that under certain pathologic conditions this circulation assumes an important function. Inflammatory conditions of the lung such as suppuration,[27, 45, 75] tuberculosis,[22, 75, 76] and bronchiectasis[39] are accompanied by enlargement and tortuosity of the bronchial arteries and the development of wide precapillary anastomoses between bronchial and pulmonary arterial circulations. Similar changes are also encountered in conditions interfering with pulmonary arterial blood flow such as certain types of congenital cardiac disease,[15, 20, 24, 43] pulmonary embolism and infarction,[45, 67, 71-73] and experimental pulmonary arterial ligation.[8, 40, 45, 62, 63] Tumors of the lung are said to be associated with an increased bronchial arterial circulation.[75, 76]

EXPERIMENTAL OCCLUSION OF THE BRONCHIAL ARTERY

Experimental attempts to obliterate the bronchial arterial circulation have on the whole been inconclusive or unsuccessful. Karsner and Ash[32] attempted to obliterate the bronchial arterial circulation to one lung of a dog by ligating en masse all the branches of the aorta below the left subclavian artery, including the second pair of intercostals. They encountered no significant gross or his-

tologic changes in the lung four weeks postoperatively. According to Sauerbruch[64] Nissen, working in his laboratory, demonstrated experimentally that ligation of the bronchial artery and of the bronchus leads to necrosis of the lung. The published report of this work[56] pointed out that the bronchi of various animals were constricted with a ligature. As will be pointed out, it is doubtful if systemic blood can be prevented from reaching the lung by this method. It is likely that the results were secondary to the bronchial obstruction.

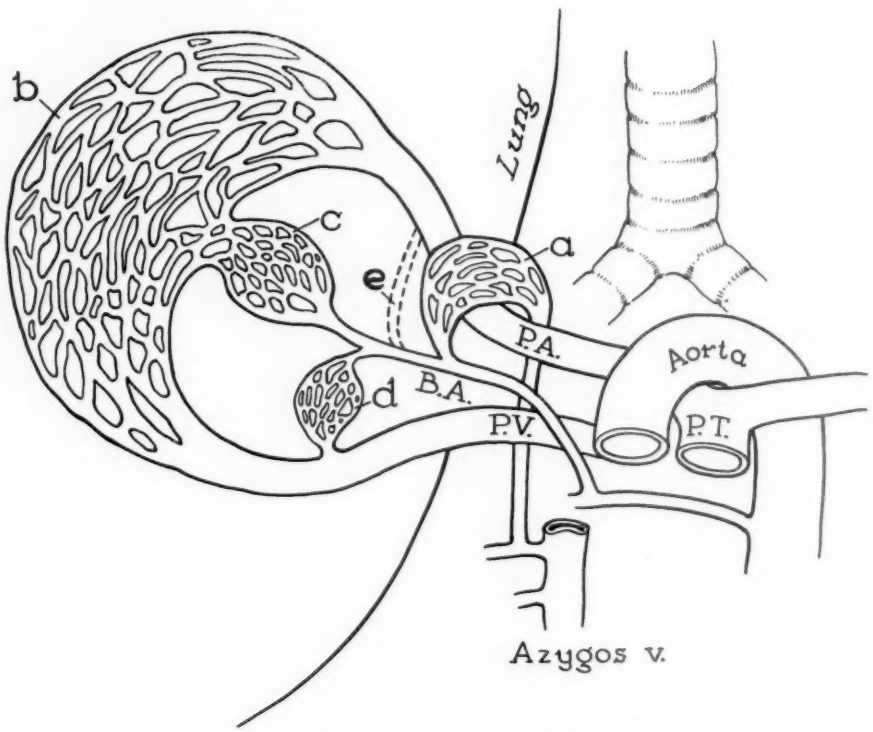

Fig. 1.—Diagrammatic sketch of the blood supply of the lung. *B.A.*, bronchial artery; *P.A.*, pulmonary artery; *P.V.*, pulmonary vein; *a*, hilar capillary plexus connecting bronchial artery and bronchial veins; *b*, pulmonary capillary plexus; *c*, bronchial capillary plexus communicating with *b*; *d*, bronchial capillary plexus communicating with pulmonary vein; *e*, precapillary anastomosis between bronchial artery and pulmonary artery, present in man but not in the dog.

Underhill[68] considered that the bronchial arterial circulation had been successfully occluded experimentally in a dog by ligation of all the structures going to the lung except the veins and the bronchus. No follow-up studies were reported. The efforts of Bruns and Sauerbruch to ligate the bronchial arteries experimentally were unsuccessful, according to Smirnow.[66] This investigator claimed, however, that he was able to occlude these vessels successfully by ligating en masse on the dog's bronchus all the bronchial vessels to a lobe. He tested the reliability of this method by injection studies in post-mortem specimens. The only changes encountered were those due to partial obstruction of the bronchus. When the pulmonary artery was ligated simultaneously, gangrene of the lobe occurred.

The experiences of Mathes and co-workers[45] with this problem are of particular significance because roentgenograms of the lung were made following the injection of Hill's mass into the aorta after death of the experimental dogs. Using this as a test of the success of the ligation these workers concluded that it is impossible successfully to occlude the bronchial arterial supply to the lung because of the multiple vessels and the free anastomoses and deep situation of the bronchial arteries as they run from the aorta to the lung within the bronchial walls. Ligation of the bronchial artery, ligation of the main arteries arising from the aorta, and stripping of all the loose areolar tissue from around the pulmonary artery, the pulmonary vein, and the bronchus failed to obliterate this circulation.

Lemoine[37] attempted to obliterate the bronchial arterial supply to the lung in a large series of dogs by a variety of means, including division of the bronchial arteries on the bronchus, stripping the bronchus free of vessels and areolar tissue, and ligation of the branches of the aorta going to the lung. No changes attributable to bronchial arterial ligation were encountered. Because of the many origins and free communications of these vessels, Lemoine attempted to occlude them by the injection of microscopic particles into the bronchial artery. This method also was unsuccessful.

While studying the effect of pulmonary arterial ligation in the dog Dargent and Berard[19] noticed autolysis of the left apical lobe four to eight days following ligation of the pulmonary artery to this lobe. Roentgenograms of the lung following injection into the aorta of a radiopaque medium, however, revealed absence of the bronchial arterial circulation in the involved lobe. This is the only hitherto reported instance with experimental evidence to prove that the bronchial arterial circulation was actually occluded. However, no studies were done in which occlusion of the bronchial arteries was carried out without concomitant pulmonary arterial ligation.

Bruns and Sauerbruch[11] suggested occluding the bronchial arterial circulation in cases of clinical tuberculosis but stated it would be extremely difficult if not impossible because of the variations in origin and the numerous anastomoses of these vessels with each other and with mediastinal and esophageal arteries. In certain reported cases,[23, 56, 64] however, there is some evidence that impairment of the bronchial arterial circulation occurred but in each case the pulmonary arterial blood flow also was probably impaired.

The experimental and clinical evidence suggests that obliteration of the bronchial arterial circulation is a difficult if not an impossible task. Ligation of the bronchial arteries is unsuccessful because of the free anastomoses with esophageal, mediastinal, and intercostal arteries. The work of Mathes and coworkers[45] has shown conclusively that dissection and ligation of vessels and areolar tissue from all the hilar structures fails to obliterate the systemic blood supply to the lung. With the exception of the experiences of Dargent and Berard[19] there is no evidence that the bronchial arterial circulation has ever been successfully occluded.

TECHNIQUE OF THE PRESENT EXPERIMENTS

A study in the dog of the effects of occlusion of the bronchial arterial circulation in its entirety by a plastic preparation was undertaken. The animals in these experiments were divided into two groups. Group 1 consisted of those dogs in which the entire right bronchial arterial system was occluded. Group 2 consisted of those animals in which only the bronchial artery of the right apical lobe was occluded.

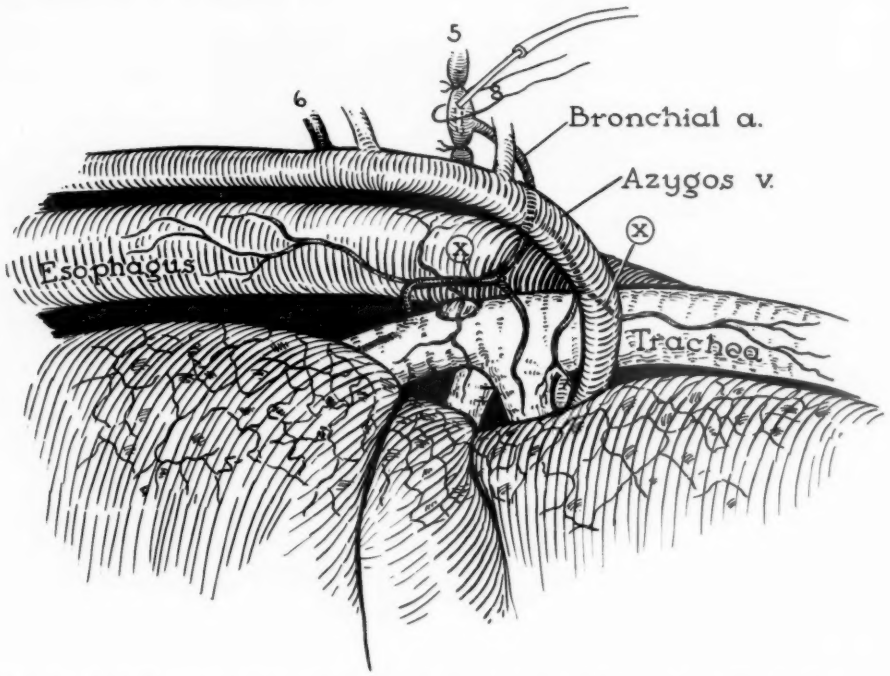

Fig. 2.—Artist's conception of dog's right posterior hilar region illustrating anatomy of the right posterior bronchial artery and the injection technique employed. *x*, location of ligatures in experiments of Group 2. The numbers indicate the corresponding intercostal arteries.

Mongrel dogs varying in weight from 12 to 21 kg. were used in this study. Preliminary anatomic studies of the origin and course of the right posterior bronchial artery were carried out. The right side was chosen because previous reports[7, 10, 40] indicated that the origin of this vessel is more constant than the origin of the bronchial arteries on the left side. Right anterior bronchial arteries from internal mammary and pericardial arteries contribute negligible amounts of blood to the lung in the presence of a right posterior bronchial artery,[10] the latter usually being the main channel of bronchial arterial supply.

In fifty of eighty-eight dogs studied, the right posterior bronchial artery arose from the right fifth intercostal artery (Fig. 2). In thirty-three it arose from the sixth intercostal artery and in one it arose from the fourth intercostal artery. In two cases it arose from the aorta in common with the right eighth intercostal artery. In two animals no such vessel was encountered. Accessory bronchial arteries were encountered in seven cases, arising from the aorta at the level of the sixth, seventh, or eighth intercostal arteries.

The origin of the right posterior bronchial artery from an intercostal artery facilitates its cannulation for the purpose of injecting material into it. Previous studies have shown the difficulties involved in occluding the bronchial arterial circulation.[32, 37, 45] It was felt that obliteration of this vessel throughout its entire length rather than its focal occlusion would present a solution to the problem. A fluid plastic preparation, vinyl acetate,* which hardens on exposure to moisture, was chosen. This preparation was found to penetrate the arterial system as far as vessels measuring about 35 μ in diameter. No recognizable systematic reaction occurred following its injection into dogs and only a mild local reaction was produced when it was injected subcutaneously into guinea pigs.

With the animal under ether anesthesia, the right thoracic cavity was entered, the right posterior bronchial artery identified, and its parent intercostal artery dissected free. This occasionally necessitated division of the sympathetic chain, the azygos vein, and adjacent intercostal vein. The intercostal artery giving rise to the right posterior bronchial artery was ligated laterally at the level of the sympathetic chain and medially, proximal to the origin of the bronchial artery. As indicated in Fig. 2 the cannula was inserted between these ligatures and ligated in place. In this manner the plastic material could be injected into the bronchial artery. One-half to 1 c.c. of vinyl acetate was injected. When injection into the entire right posterior bronchial artery was planned, the main esophageal branches of the bronchial arteries were ligated prior to injection. When injection into branches to the right apical lobe only was planned, additional ligatures were placed around the bronchial arterial branches to the trachea and around the right posterior bronchial artery distal to the origin of the branch or branches to the right apical lobe (Fig. 2).

Duracillin was administered intramuscularly in doses of 1 c.c. per day for the first two to five postoperative days. Serial roentgenograms of the thorax were made and post-mortem examination was carried out as soon after death as possible. At necropsy, the trachea, both carotid, and both axillary arteries were ligated. The aorta was clamped at the level of the diaphragm and then 100 c.c. of a mixture containing 40 per cent barium sulfate and 12.5 per cent gelatin was injected into the ascending aorta. The thoracic viscera were then removed from the thoracic cavity, care being taken to prevent escape of the injected radiopaque medium. Roentgenograms were then made of the lungs. By utilizing this technique the lungs could be examined grossly, microscopically, and roentgenographically to determine the completeness of the bronchial arterial occlusion and the presence or absence of collateral systemic vessels to the lobe or lung with occluded bronchial arteries. After roentgenography, the lungs were preserved in a 1:10 solution of formaldehyde and sections cut from representative parts were prepared, after paraffin imbedding, and stained with hematoxylin and eosin; in certain instances Verhoeff's elastic tissue stain, with van Gieson's connective tissue stain used as counterstain, was also employed. Frozen sections were made to visualize the vinyl acetate solution within the bronchial arteries.

*Ward's Vinyl Acetate, from Ward's Natural Science Establishment, Inc., Rochester, N. Y.

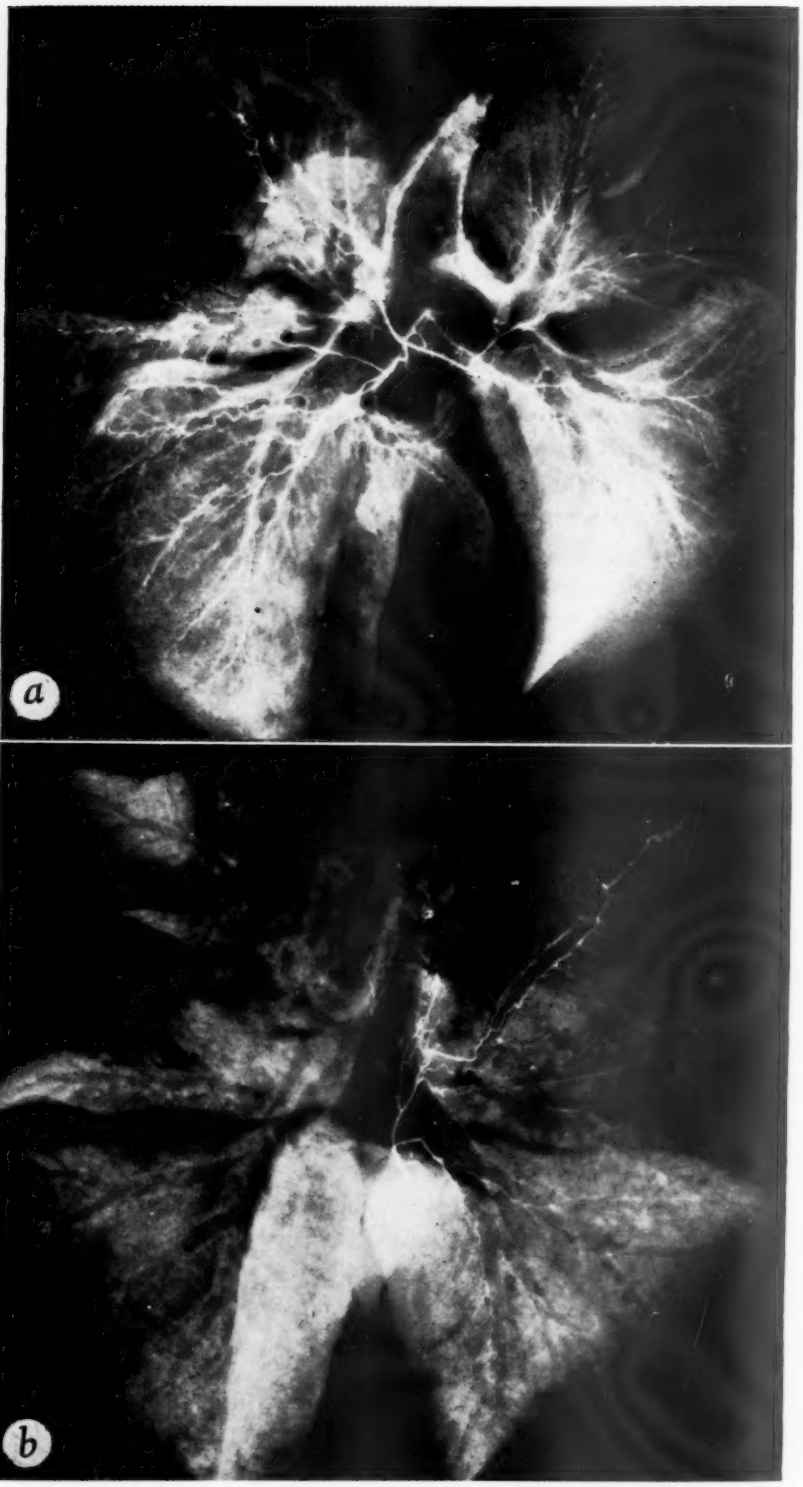

Fig. 3.—*a*, Post-mortem roentgenogram of a dog's lungs as viewed from in front demonstrating normal bronchial arterial circulation which had been filled with barium sulfate-gelatin suspension. *b*, Similar roentgenogram of the lungs of a dog of Group 1, five days after right posterior bronchial arterial occlusion. Normal bronchial arterial circulation is present only on the left side.

RESULTS

Group 1, Occlusion of the Entire Right Posterior Bronchial Artery.—The five dogs comprising Group 1 had the entire right lung deprived of its bronchial arterial supply by the method described. Postoperatively the animals showed progressive respiratory distress and fever. There were no survivals of longer duration than a week.

Fig. 4.—Bifurcation of the opened trachea viewed from in front. There is ulceration of the right stem bronchus and of the right lobar bronchi in the region of the hilum five days after occlusion of the right posterior bronchial artery in a dog of Group 1.

Post-mortem roentgenograms of the removed lungs following the injection of barium sulfate-gelatin suspension into the aorta demonstrated in each case the absence of barium-filled bronchial arteries on the right side. A dog's normal bronchial arterial circulation as delineated by the radiopaque medium is seen in Fig. 3, *a*. Fig. 3, *b* is a post-mortem roentgenogram of a dog's lungs in which the right posterior bronchial artery had been occluded by vinyl acetate. The absence of barium-filled vessels on the right is apparent, whereas the normal bronchial arterial pattern is present on the left.

On gross examination both lungs were heavy, edematous, and mottled. On section, varying degrees of ulceration of the right main stem bronchus and of the lobar bronchi for a distance of a few millimeters from their origin were encountered (Fig. 4). In three instances, small areas of infarction and ulceration of the mid-portion of the esophagus were also present.

On microscopic examination, the right stem bronchus and the right lobar bronchi in the region of the hilum showed evidences of infarction and ulceration (Fig. 5). Parabronchial lymph nodes in this region were infarcted. Distal to the right hilar region the bronchi were viable. Here there was mild submucosal congestion (Fig. 6, *a*).

In none of the sections prepared from the right lungs of dogs of Group 1 did the bronchial arteries contain barium which had been injected into the aorta after death. On the left side not only were bronchial arteries filled with barium regularly encountered but none of the necrotizing changes of the bronchial wall mentioned for the right lungs was present (Fig. 6, *b*). Both right

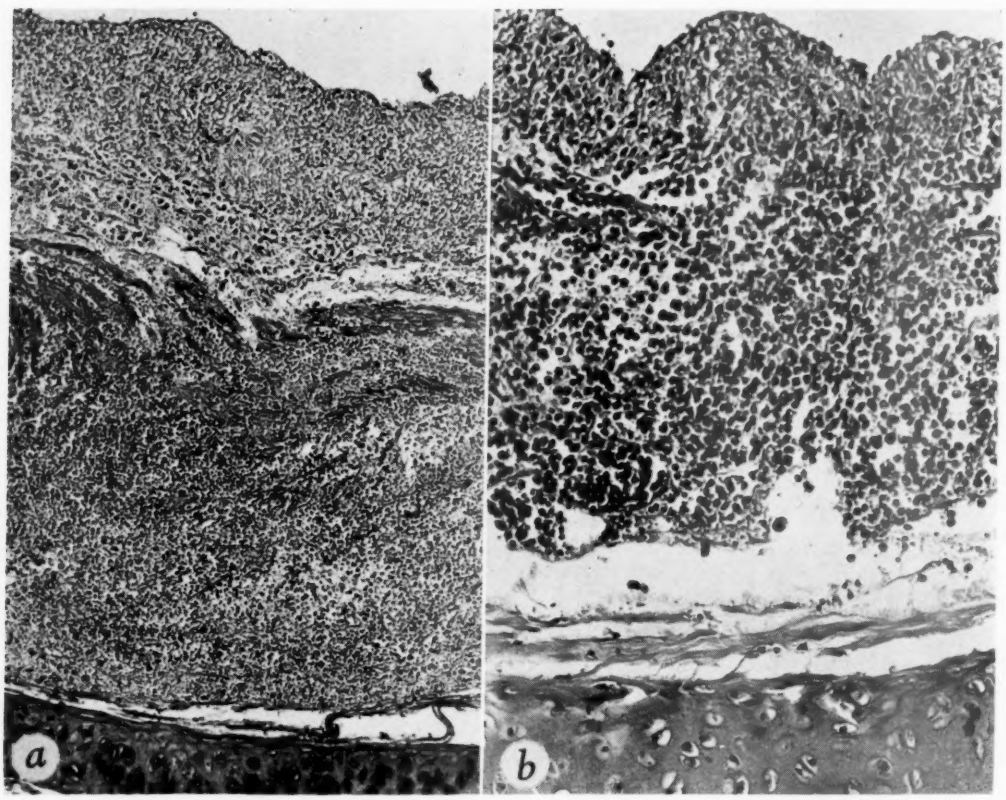

Fig. 5.—*a*, Section from a right lobar bronchus after occlusion of the right posterior bronchial artery in a dog of Group 1. Infarction of the bronchial wall and ulceration of the mucosa are present (hematoxylin and eosin, ×90). b, A similar area in another dog of Group 1 (hematoxylin and eosin, ×170).

and left lungs in all dogs exhibited an extensive pneumonic process. There was no apparent difference in the intensity of the disease in the right lung as compared to the left lung, the latter during life having retained its normal systemic blood supply.

Group 2, Occlusion of the Bronchial Arterial Branches to the Right Apical Lobe.—Eight dogs comprised Group 2. In these, occlusion of the bronchial arterial supply to the right apical lobe was performed. All animals survived the operative procedure and there were no postoperative deaths. At selected times the animals were killed by exsanguination while under anesthesia. The shortest period of postoperative study was three and one-half weeks, and the longest a year.

With one exception no abnormality of the right apical lobe could be detected either grossly or microscopically. Post-mortem roentgenograms of the lungs

following injection of barium sulfate-gelatin suspension into the aorta after death revealed in all cases but one the absence of barium-filled vessels in the right apical lobe (Fig. 7). Further evidence that no systemic blood reached the right apical lobe during life through vessels larger than 30 to 35 μ in diameter* was obtained in seven of the dogs by gross and microscopic examination of the tissues. Grossly, only the injected plastic could be seen in the vessels of the bronchial wall of the right apical lobe, whereas barium-filled bronchial arteries could be seen entering the remaining lobes. Microscopic examination

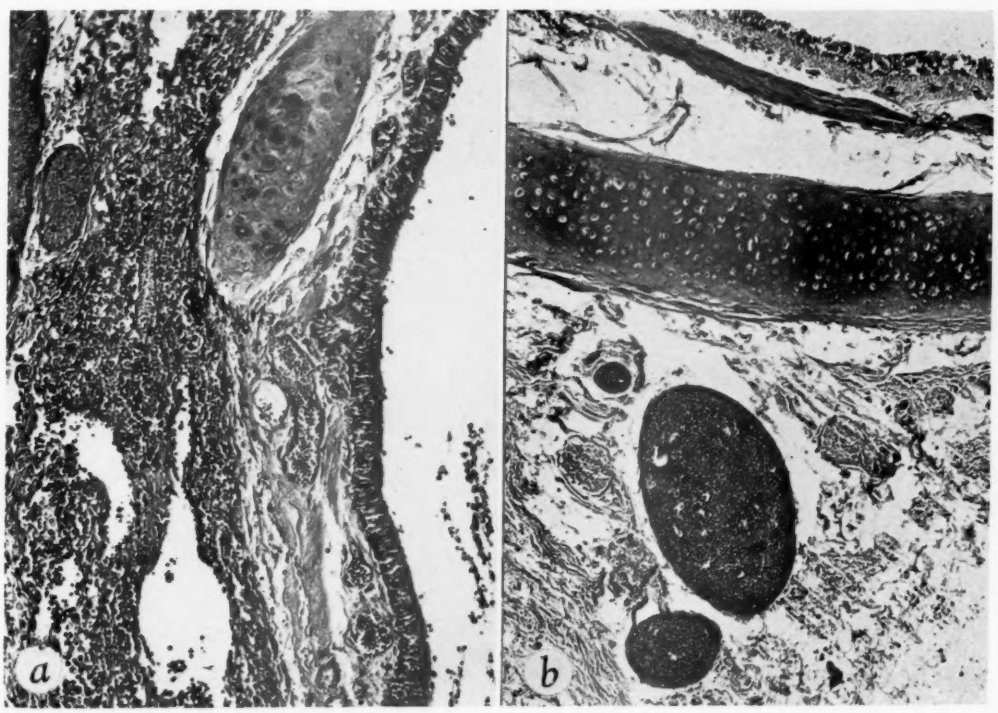

Fig. 6.—*a*, Section from a right secondary bronchus of a dog of Group 1 showing viable bronchial wall with submucosal congestion (hematoxylin and eosin, ×80). *b*, Section from the proximal portion of a left lobar bronchus of a dog of Group 1 five days after occlusion of the right posterior bronchial artery. The bronchial wall appears normal. Three barium-filled vessels are seen beneath the cartilage (hematoxylin and eosin, ×60).

of frozen sections of the right apical bronchus showed the main bronchial arteries and their branches to be filled with the blue-colored plastic which had been injected at operation (Fig. 8, *a*). No barium-filled vessels were seen except occasionally adjacent to a normally appearing hilar lymph node. The latter finding is in contrast to the infarcted right hilar lymph nodes encountered in Group 1.

The one exception mentioned above is worthy of special note. An increased density developed in the right upper pulmonary field on roentgenographic examination two months postoperatively. This persisted until the animal was killed under anesthesia four months later. At post-mortem examina-

*The barium sulfate-gelatin suspension employed did not penetrate vessels smaller than 30 to 35 μ in diameter.

tion the right apical lobe was hard, nodular, and discolored. Section of the lobe revealed bronchial atresia and extensive bronchiectasis. Post-mortem roentgenograms of the lung following the injection of barium sulfate-gelatin suspension into the aorta showed that in spite of the operative occlusion of the systemic blood supply to this lobe an extensive collateral systemic circulation existed at the time of death. On further examination it was apparent that the bronchial artery of the right cardiac lobe had also been occluded at the time of the initial injection.

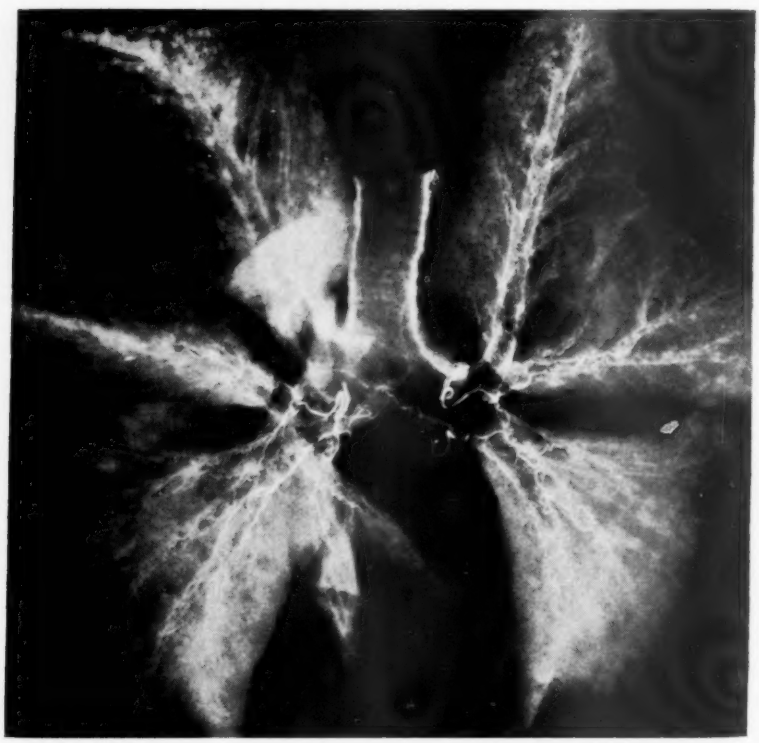

Fig. 7.—Post-mortem roentgenogram, viewed from in front, of the lungs of a dog of Group 2 in which the bronchial artery of the right apical lobe was occluded three months previously. Normal bronchial arterial circulation is seen in all but the right apical lobe.

The experiments performed on dogs of Groups 1 and 2 suggested that the pulmonary arterial blood was nourishing the pulmonary parenchyma and the bronchial wall distal to the hilum after the obliteration of the bronchial arterial circulation. To ascertain whether or not pulmonary arterial blood could actually reach the capillaries of the bronchial wall when the main bronchial arteries to the right apical lobe were occluded, the following experiment was carried out. Two of the animals in Group 2, one ten and one-half months and the other one year after operation, were selected. A solution of Higgins India ink diluted 1:10 in saline solution was injected into the pulmonary arteries of these animals after death and sections taken from the bronchi of the right apical lobes. The India ink was clearly evident in the capillaries and smaller arterioles of the bronchial wall (Fig. 8, *b*). Thus, in these two dogs, it was demonstrated that pulmonary arterial blood could reach the bronchial wall.

COMMENT

The cause of death of the animals in Group 1 in which the bronchial arterial supply to one entire lung was occluded appeared to be an overwhelming pneumonia secondary to infarction and ulceration of the bronchus. One might have expected pneumonia not to have developed in the opposite lung, retaining as it did its normal systemic blood supply. Presumably the pneumonic process spread rapidly to the opposite lung from the lung with its bronchial arterial supply obliterated.

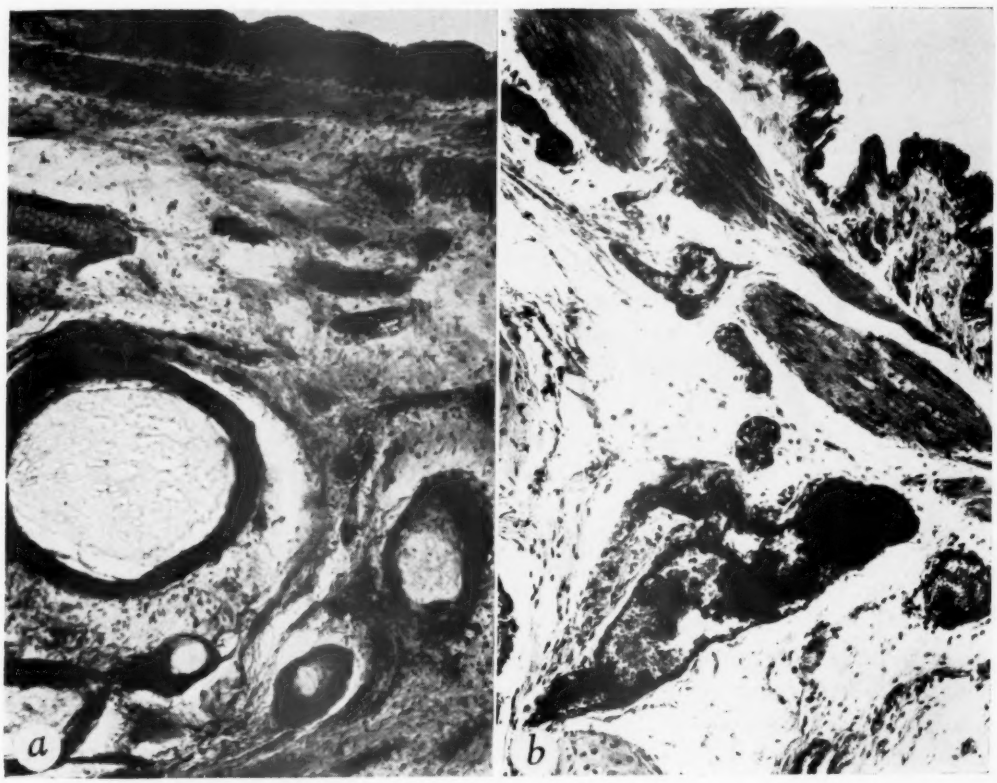

Fig. 8.—*a*, Section from a secondary bronchus of the right apical lobe of a dog of Group 2 showing vinyl acetate in the lumina of arteries of the bronchial wall. There is lack of reaction around the vessels (hematoxylin and eosin, ×80). *b*, Section from a secondary bronchus of the right apical lobe of a dog of Group 2. India ink, which had been injected into a pulmonary artery, is present in the bronchial vessels (hematoxylin and eosin, ×312).

No infarction or ulceration was noted in the lobar bronchi farther than a few millimeters from their origin. The bronchi distal to the hilar region were normal except for some submucosal congestion. To explain the restricted area of infarction and ulceration, certain points of the vascular anatomy of the lung already mentioned must be emphasized (Fig. 1). From the region of the hilum of the lung, blood brought by the bronchial arteries is returned to the right atrium by bronchial veins and there is no direct communication with the pulmonary arterial system. From the other portions of the lung, blood delivered by the bronchial arteries is returned to the left atrium by the pulmonary veins.

Therefore, except in the hilar region, a functional anastomosis between bronchial and pulmonary vascular systems exists. It is possible that preservation of viability of the lobar bronchi depended upon blood coming from the lesser circulation through the joint capillary system common to both circulations.

A similar explanation may account for the lobes which appeared normal following occlusion of the bronchial artery to the right apical lobe in the Group 2 series of experiments. In this group, however, there was no evidence of infarction or ulceration of the bronchus in the hilar region except in one instance.

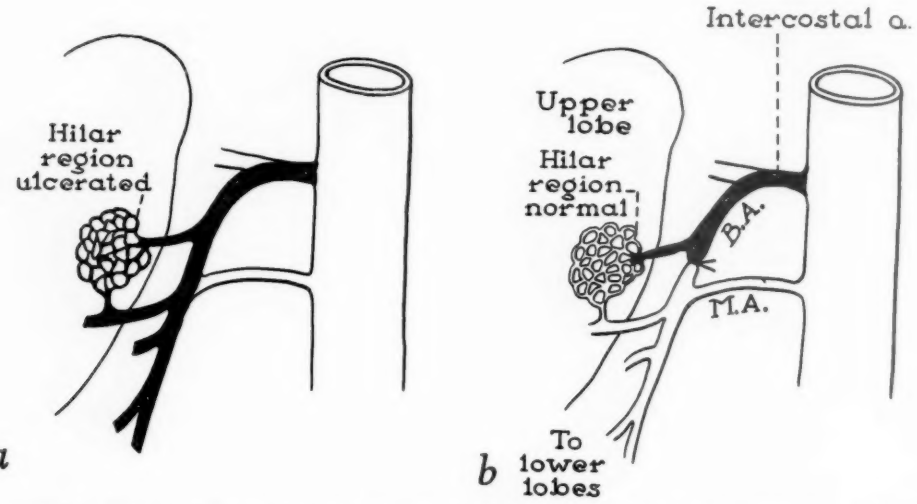

Fig. 9.—*a*, Extent of bronchial arterial occlusion in Group 1 experiments. *b*, Extent of bronchial arterial occlusion in Group 2 experiments. *B.A.*, bronchial artery; *M.A.*, mediastinal collateral arteries. A collateral blood supply was available to the uninjected vessels of the Group 2 dogs through the mediastinal collateral arteries.

For any animal to have escaped infarction and ulceration of the hilar bronchi, systemic blood from other sources must have been available as a supply for this area. The presence of barium-filled vessels near normal hilar lymph nodes adjacent to lobes whose bronchial arteries had been occluded indicated that systemic blood was supplying the hilar region. On the other hand, infarction of the hilar lymph nodes did occur in the Group 1 series of experiments. The logical source of blood supplying the hilar region in the animals of Group 2 would have been the adjacent normal bronchial arteries. Fig. 9 illustrates diagrammatically the difference in the extent of the bronchial arterial occlusion in the dogs of Group 1 as compared with that of Group 2, and offers an explanation for the different results obtained in these two groups.

In the one animal in Group 2 that exhibited acquired bronchial atresia and extensive bronchiectasis, the bronchial atresia may have developed secondary to bronchial ulceration. Post-mortem roentgenograms of this dog's lungs following injection into the aorta of barium sulfate-gelatin suspension revealed that the right cardiac lobe also had been deprived of its bronchial arterial supply. In other words, the initial occlusion of bronchial arterial circulation involved two lobes instead of one. This additional area of occluded bronchial

arterial supply to the hilar region with attendant loss of collateral supply to the apical lobe could well explain the development of bronchial infarction leading finally to the observed atresia. Despite the bronchial arterial occlusion, an abundant new systemic arterial supply ultimately developed to this dog's right apical lobe where an extensive bronchiectatic process had developed.

Before drawing definite conclusions regarding the importance of the bronchial arterial circulation from the experimental data available, certain sources of possible error in the techniques employed must be evaluated. Were the bronchial arteries occluded by the methods used? The technique of examining the lungs at post-mortem, grossly, microscopically, and roentgenographically after injection into the aorta of a radiopaque medium, provided as accurate a check as possible on the success of the experimental occlusion. Any systemic blood that continued to supply such a lobe must of necessity have reached the lobe through vessels smaller than 35 μ, for all larger vessels had been experimentally occluded.

Could the injection fluid itself, vinyl acetate, have had a role in producing the observed results? Preliminary studies showed that the local tissue reaction to this preparation was minimal. Frozen sections showing this material in the bronchial vessels failed to reveal any significant inflammatory reaction in the surrounding tissues and the plastic material was never observed to enter vessels smaller than 35 μ in diameter.

On the assumption that the experimental criteria were successfully met by the methods used, certain conclusions can be made as follows:

1. The bronchial arteries are necessary for the nutrition of the main stem bronchus and of the lobar bronchi in the region of the hilum.

2. A dual blood supply exists for the pulmonary tissues and bronchi peripheral to the hilum. In the absence of a bronchial arterial supply, the lobar bronchi retain their viability except for a few millimeters from their origin.

It is of interest that recent structural studies have shown that the size of the bronchial arteries of the human fetus is nearly the same as that of the adult, whereas a great expansion occurs in the pulmonary vascular system after birth.[44] The bronchial arteries may then be considered as a vestigial circulatory system, important in the fetus before birth but of little significance under normal conditions after birth except in the region of the hilum. When pathologic processes involve the lung this vestigial blood supply may again be called upon to fulfill an important nutrient function.

SUMMARY AND CONCLUSIONS

These experiments were undertaken for the purpose of investigating the importance of the bronchial arterial circulation in the normal dog's lung. Anatomic studies of the origin of the dog's right posterior bronchial artery were made and a method was devised for successfully occluding the bronchial arterial circulation by the injection of vinyl acetate.

In all animals subjected to occlusion of the right posterior bronchial artery, infarction and ulceration of the right stem bronchus and the right lobar bronchi in the hilar region developed. Distal to the hilum the bronchi remained normal. All animals of this group died of bilateral bronchopneumonia. When only the bronchial artery to the right apical lobe was occluded, the animals survived and with one exception no pathologic changes were encountered within the operated lobes. In one dog bronchial atresia and bronchiectasis developed secondary to an ulcerative process in the wall of the hilar portion of the right apical lobar bronchus. The bronchial arterial occlusion in this instance was more extensive than in the case of the other animals of this group.

It is apparent from these studies that, in the dog, the bronchial arteries are necessary for the nutrition of the main stem bronchi and the lobar bronchi in the region of the hilum. Blood supplied by the pulmonary artery can maintain the integrity of the pulmonary tissue and the bronchial walls distal to the hilar region. Bronchial arterial circulation is not necessary under normal conditions in these latter parts. An explanation is offered for the variable role played by the bronchial arterial circulation in nourishing separate parts of the bronchial tree. This explanation is based on differences in the intrinsic anatomy of the bronchial arteries encountered in these separate locations.

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THE INCIDENCE OF DISTANT METASTASES AMONG PATIENTS DYING WITH HEAD AND NECK CANCERS

An Analysis of 200 Autopsies

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INTRODUCTION

IS CANCER of the head and neck a localized disease? How frequently do these tumors spread below the clavicle? The answers to these question bear directly upon the problem of therapy, for in the absence of distant metastases, local excision can be carried out radically with hope for success. For many years the incidence of remote metastases among patients with head and neck cancers has been considered to be very low. In 1906, in an article describing the method of radical neck dissection which bears his name, Crile[3] laid the foundation for this belief: "A careful study of 4,500 cases, exclusive of the thyroid gland, traced to their original report in literature, made for me by Dr. C. F. Hitchings, showed that in less than 1 per cent have secondary foci been found in distant organs and tissues." It is unfortunate that Hitchings never published a report of his study. At a Symposium on Carcinoma of the Jaws, Tongue, Cheek and Lips[6] held in 1923, the general consensus of the distinguished surgeons present was that distant metastases from cancers of the head and neck were very rare. Ewing,[4] as late as 1941, also held this opinion. In the meantime, reports of a higher incidence of such metastases have appeared. Price[5] performed autopsies upon 87 patients with squamous-cell carcinomas of the tongue, lip, floor of the mouth, and pharynx, and found 10 (11 per cent) with distant metastases. Willis reported 2 series of 62 autopsies performed upon patients with cancers of the head and neck. Of these, 24 (38 per cent) proved to have remote metastases. Among 31 patients with squamous-cell cancers of the lip, tongue, pharynx, and antrum coming to autopsy, Burke[2] found distant metastases in 11 (39 per cent). In a group of 174 patients with head and neck cancers autopsied at Memorial Hospital, Braund and Martin[1] found 36 (20 per cent) with distant metastases. In an effort to reconcile, if possible, these divergent opinions and to determine the incidence of such remote metastases in our own material, we have reviewed all autopsies performed upon patients dying with head and neck cancers. The results of this study form the substance of this report.

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CHARACTERIZATION OF THE MATERIAL

A careful sifting of the records of the Department of Pathology, University of Minnesota, through the years 1920 to 1950 produced the records of 200 patients in whom malignant epithelial tumors arising in the head and neck were present at the time of death. Cases of basal-cell carcinoma, carcinoma of the thyroid, intrinsic tumors of the larynx, melanoma, and lymphoblastoma have been excluded. One patient had a cancer of the lip coincidental with a cancer of the tonsillar fossa, making a total of 201 tumors in 200 patients. The exact location of the primary tumor could be determined accurately in all but a few patients in whom the extent of the tumor made exact localization impossible. In these cases, the history and hospital record furnished the required information.

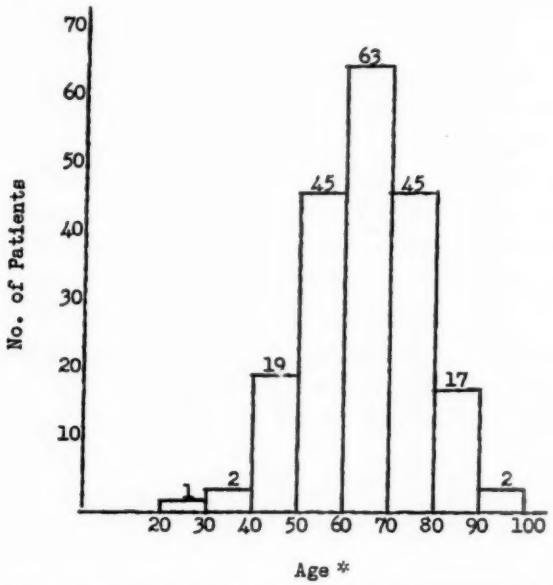

Fig. 1.—The age distribution of 200 patients with cancers of the head and neck. *The age of six patients could not be determined.

A complete examination of the head, the neck, and the viscera was made in each case. Examination of the cadaver was frequently supplemented by roentgenograms made prior to death. The presence of metastases was determined by gross examination at autopsy, and in each case material for microscopic examination was taken. The results of our study can be divided into two parts: the first is concerned with the 200 patients as a whole, the second, with those patients in whom distant metastases were detected.

THE GROUP AS A WHOLE

Of the 200 patients, 187 were males, only 13 females. The age distribution of the patients is shown in Fig. 1. The location of the primary tumors and the incidence of regional (i.e., cervical) lymph node metastases are shown in Table I. Of special interest is the tabulation of the immediate causes of death in these

patients (Table II), since a clear understanding of the final episode makes for more effective palliative care in advanced cases.

THE GROUP WITH DISTANT METASTASES

At autopsy 36 of the 200 patients were considered to have distant metastases originating from a primary cancer of the head or neck. These cases were subjected to scrutiny, with a correlation of all of the information available in the

TABLE I. LOCATION OF THE PRIMARY TUMOR AND INCIDENCE OF CERVICAL NODE INVOLVEMENT IN 200 CASES OF CANCER OF THE HEAD AND NECK

PRIMARY TUMOR	NUMBER OF CASES	NUMBER OF CASES WITH INVOLVEMENT OF CERVICAL LYMPH NODES
Lower lip	44	26
Tongue	46	32
Buccal mucosa	13	9
Upper Alveolar ridge	2	0
Lower	16	8
Tonsillar fossa	15	14
Palate	3	2
Floor of mouth	3	2
Nasal cavity	3	2
Nasopharynx	3	3
Maxillary sinus	12	5
Pharynx	20	14
Skin of face	11	6
Parotid	2	1
Lacrimal gland	2	1
Unknown primary	6	6
Total	201*	131

*One patient had a cancer of the lip and of the tonsillar fossa.

TABLE II. IMMEDIATE CAUSES OF DEATH IN 200 PATIENTS WITH CANCERS OF THE HEAD AND NECK

RESPIRATORY COMPLICATIONS		COMPLICATIONS ASSOCIATED WITH TUMOR GROWTH		UNRELATED CAUSES OF DEATH	
Pneumonia	89	Carotid thrombosis	2	Subacute bacterial endocarditis	1
Lung abscess	6	Hemorrhage	21	Heart failure	3
Pulmonary edema	8	Cellulitis	6	Coronary occlusion	5
Laryngeal edema	6	Meningitis	4	Cerebrovascular accident	1
Respiratory obstruction	7	Cerebral edema	2	Pulmonary embolism	2
Respiratory failure	1	Cachexia	15	Accidents	2
Anesthetic death	3	Carcinomatosis	3	Tuberculosis	6
				Perforated duodenal ulcer	1
				Bleeding duodenal ulcer	1
				Portal thrombosis	1
				Pyelonephritis	1
				Renal carbuncle	1
				Peritonitis	1
				Carcinoma of lung	1
Totals	120		53		27

protocol, the hospital records, and the preserved pathologic material. Two cases were discarded: one, because no convincing evidence of remote metastasis could be established, another, because histologic examination of the liver metastasis

TABLE III. LOCATION OF THE PRIMARY TUMOR AND ITS METASTASES IN 34 CASES OF CANCER OF THE HEAD AND NECK

PRIMARY	NUMBER OF CASES	PER CENT OF TOTAL GROUP	LYMPH NODE INVOLVEMENT			LUNG	LIVER	ADRENAL	HEART	BONES*	PANCREAS	KIDNEY	SPLEEN
			CERVICAL	THORACIC	ABDOMINAL								
Lower lip	4	9	4	2	1	1	2		2				1
Tongue	6	13	6	1		6	1	1	4	1		1	1
Buccal mucosa	3	23	3	1		1	1		1				
Alveolar ridge	2	11	1			2							
Tonsillar fossa	2	13	2	1		1						1	
Palate	1	33	1						1				
Floor of mouth	1	33	1	1		1							
Nasal cavity	3	100	1			2	2	2		1			
Nasopharynx	1	33	1		1		1						
Maxillary sinus	3	25	2	1	1	1	3	1		1	1		
Pharynx	3	15	2		1	3	3	2		1		1	
Parotid	1	50				1							
Lacrimal gland	1	50	1	1		1					1		
Unknown primary	3	50	3		1	1	3	1		1		1	
Totals	34	17	28	8	5	21	16	7	8	5	2	4	2

The axillary node, the esophagus, and the diaphragm were each involved once.

*The bony metastases were found in the spine (3), the ribs (4), and the sternum (1).

revealed an adenocarcinoma of intestinal origin. In the remaining 34 cases, there was satisfactory evidence that we were dealing with a tumor of the head and neck which had metastasized below the clavicle. The locations of the primary tumors and their distant metastases are shown in Table III. Of particular interest are (1) the high incidence of cervical node involvement among patients with remote metastases (28 of 34 cases), and (2) the number of metastases to the myocardium. The histologic character of the metastasizing tumors is indicated in Table IV. Thirty-one of the tumors were squamous-cell carcinomas. No attempt has been made to grade these tumors histologically except to note the presence or absence of cornification. Two cylindromas were encountered: one in the lacrimal gland, the other in the tongue. The remaining tumor was an adenocarcinoma of the parotid.

TABLE IV. HISTOLOGIC CHARACTER OF THE 34 METASTASIZING TUMORS

PRIMARY SITE	TOTAL NUMBER	SQUAMOUS CELL CARCINOMA		CYLINDROMA	CARCINOMA
		WITH CORNIFICATION	WITHOUT CORNIFICATION		
Lower lip	4	4			
Tongue	6	2	3	1	
Buccal mucosa	3	3			
Alveolar ridge	2		2		
Tonsillar fossa	2	1	1		
Palate	1		1		
Floor of mouth	1	1			
Nasal cavity	3		3		
Nasopharynx	1		1		
Maxillary sinus	3	1	2		
Pharynx	3		3		
Parotid	1				1
Lacrimal gland	1			1	
Unknown primary	3	1	2		
Totals	34	13	18	2	1

DISCUSSION

The age distribution of these patients and the great preponderance of males are characteristic of patients with head and neck cancers. The proportionate incidence of the various primary tumors in this group conforms rather well to the incidence of similar tumors among living clinic patients. Thus, it provides a reasonable sample of head and neck cancer for determining the incidence of distant metastases. Examination of the immediate causes of death in these patients focuses attention upon the close association between disturbances in the anatomy and function of the pharynx, produced by contiguous tumor growths, and the high incidence of fatal pulmonary complications. Unchecked local extension of tumor growth, infection, and necrosis lead inexorably to hemorrhage, cellulitis, and occasionally meningitis. The cachexia encountered in these patients is not usually related to the wide dissemination of metastases but rather to difficult and painful swallowing. Unrelated causes of death are common in any group of patients of this age distribution.

The finding, in our group of 200 patients, of 34 (17 per cent) with distant metastases places our study in general agreement with similar studies to which we have previously referred.[1, 2, 5, 7] We have been impressed by the high incidence of cervical node metastases (28) in the 34 patients having distant metastases. This may be a reflection of either the advanced stage of disease at which distant metastases occur or the greater malignant potential of the tumors which metastasize. Unfortunately, information in regard to the involvement of the large veins of the head and neck by tumor was completely lacking in our material. The importance of such data becomes evident from the report of Willis,[7] who noted that in 24 patients with head and neck cancers in whom distant metastases were found, invasion of the jugular vein or its major tributaries was demonstrated in each one. It appears from an examination of the distribution of the remote metastases (Table IV) that once the tumor cells leave the neck they become widely disseminated. Lymphatic spread from the cervical lymph nodes to those of the mediastinum does not seem to be of prime importance, as only 8 of the 34 cases had involvement of these glands. Why these tumors, especially those of the lip and tongue, appear to thrive in the myocardium, a finding corroborated by others, remains an enigma.

It is of real importance to surgeons who deal with this problem, and one which should prove a stimulus to their efforts, to have statistical evidence that even at the time of death from head and neck cancer, 83 per cent of patients still have the disease confined to the relatively local area above the clavicle. Such knowledge should spur on aggressive efforts of surgeons and others to eradicate cancer in this area since the incidence of systemic spread is relatively low even at the time of death.

SUMMARY

We have examined the autopsy protocols of 200 patients with head and neck cancers and found thirty-four cases (17 per cent) with metastases below the clavicle. While this incidence is not in accord with older conceptions of the behavior of these tumors, it is in agreement with more recent studies upon similar material. Respiratory complications accounted for the immediate death of 120 of these patients. Among the thirty-four patients with distant metastases, there was cervical lymph node involvement in twenty-eight. A search should be made in operative specimens and at autopsy for evidence of invasion of the large veins of the neck by tumor.

CONCLUSIONS

In a group of 200 autopsies performed upon patients with cancers of the head and neck, thirty-four (17 per cent) were found to have distant metastases below the clavicle.

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THE EXPERIMENTAL USE OF FREE ARTERIAL AND SPLIT-THICKNESS SKIN GRAFTS FOR BRIDGING DEFECTS IN THE COMMON BILE DUCT OF THE DOG

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RECONSTRUCTION of the strictured or absent common bile duct long has been and continues to be a challenge. The many reconstructive methods which have been suggested are evidence that no satisfactory procedure has been devised. Our approach to this problem has been to investigate the feasibility of repairing artificially created common duct defects in dogs with autogenous free arterial and split-thickness skin grafts.

REVIEW OF THE LITERATURE

Numerous methods have been proposed for repair of common duct defects. Davis and Lewis (1913)[1] reported utilizing rectus fascia for this purpose in dogs. In their series four animals survived for several months with viable grafts; others succumbed from infection or biliary peritonitis. Lord and Chenoworth (1943)[2] used fascial grafts over Vitallium tubes to replace common duct defects in dogs and found this satisfactory in animals observed over a six months' period.

Sullivan (1909)[3] described a method of using small rubber tubing for bridging gaps of the common duct, and subsequently Wilms (1912)[4] attempted this procedure in human beings. Omentum was suggested by Borst and Enderlen (1909),[5] and flaps of serosal and muscular layers by Baldassari and Gardini (1913).[6] Kehr (1909)[7] devised a method of detaching serosal flaps from the stomach to replace portions of the common duct.

Lord and Chenoworth[2] tested the efficacy of free vein and peritoneal grafts over Vitallium tubes to bridge defects in the common bile ducts of dogs. They observed that a lining of biliary epithelium had developed over the intima of the vein grafts. Of ten animals in which venous grafts were used, four showed leakage. Peritoneal transplants failed in four of five animals because of leakage, obstruction, or both. When the grafts were examined at the end of the third week, no evidence of peritoneal tissue could be found. Horsley (1918)[8] inverted a segment of vein and sutured it into a defect created by resecting a portion of the common duct in dogs. After a few months the vein became contracted and completely obstructed. A series of twenty-one animals in which a common duct defect was repaired with a free vein graft over Blakemore-Lord tubes was reported by Shea and Hubay (1948).[9] In fourteen the resultant bridging channels remained functionally

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patent and maintained a flow of bile for periods up to 208 days. In nine of the fourteen with good results the original vein graft was present, and in the other five a pliable channel lined with biliary epithelium was noted. In four animals the operations were considered as failures. Three animals died from distemper in the immediate postoperative period.

Vitallium tubes were developed by Pearse (1942)[10] and have been used by many others[11, 12] since their original description. Their use in 106 human cases was reported by Pearse (1946)[13]; eighty-five of his cases had good results, twelve showed plugging of the tubes, and seven were failures. Clute (1942)[11] presented the successful use of a Vitallium tube in bridging a 2 cm. gap in a stricture of the common duct after wrapping omentum about the bare metal joining the ends of the duct. Vitallium tubes wrapped with fascia have been utilized to bridge defects in the ureter.[14] Neibling and Walters (1947)[15] discussed nine patients with plugging of Vitallium tubes postoperatively. Pearse (1946)[13] analyzed the calculous material found in Vitallium tubes which became plugged and found it composed of soluble cholesterol (36 to 56 per cent) and insoluble bile pigment with calcium. The administration of sodium taurocholate and sodium dehydrocholate postoperatively to increase the solubility of cholesterol has been attempted without any effective results.

The technique of construction and the results obtained in replacing defects of the common bile duct, the dura mater, trachea, and bronchi with Polythene have been described by Grindlay (1948).[16] He found no signs of obstruction in Polythene tubes inserted between the ends of a common duct defect in a one-year postoperative period. Polythene, a polymer of paraffin, possesses the advantage of being less irritating to tissue than many other plastic substances.

Bird quills have been experimentally investigated as prostheses for common duct repairs by Christmann and Defeo (1946-1947)[17-19] and two instances in which this material was utilized in patients with postoperative common duct strictures were discussed. In one case, calculi caused recurrent obstruction shortly after insertion of a heron quill. In the second, the patient was well one year after operation.

McCorriston and MacKenzie (1948)[20] embedded split- and full-thickness skin grafts in tubular form in the free edge of the greater omentum of rabbits and dogs. In one rabbit and one dog this was utilized in a second operation to drain bile from the gall bladder to the proximal loop of jejunum. Neither of these proved successful.

The advantages of V flap and Z plasty procedures in experimental anastomoses of the common duct of dogs were studied by Singleton and Moore (1950),[21] who recommended these plastic surgical maneuvers to obtain end-to-end anastomoses.

Recently Kirby and Fitts (1950)[22] have reported on the results of reconstructing segments of bile ducts by interposing isolated pieces of jejunum. In seven animals there was no evidence of stricture or calculus formation.

The results of most of the experimental and clinical studies searching for a suitable prosthesis for reconstruction of defects of the bile ducts have been

discouraging. The common purpose of any foreign object is to serve as a support or scaffolding while healing of adjacent or anastomosed tissues is occurring (Walters and Phillips).[23] Many of the attempted substitutes such as free vein grafts have perished because of lack of sufficient blood supply with subsequent necrosis, perforation, and fibrosis. In other instances, for example rubber, the adjacent tissue is irritated by the foreign object with fibrosis and contracture after removal of the rubber tubing. The synthetic resins, which are members of the polyvinyl series, have the disadvantage of containing plasticisers (organic solvents) which are added to give flexibility and transparency. Gradually the body fluids extract this chemical, which is not only irritating to tissues, but with its extraction, causes the plastic to become brittle and unyielding. Harder objects such as metals often cause pressure necrosis and are not easily molded. In any foreign substance this problem of calculus formation is prominent, although this may have been partially solved by the newer "non-wettable" synthetic plastics.

EXPERIMENTAL METHODS

In an attempt to determine whether or not free arterial and split-thickness autografts (skin) would prove practical for replacing defects of the common bile ducts, three series of dogs were studied under varying conditions. In the first group a free arterial autograft approximately 3 to 4 cm. long was taken from the superficial femoral artery. After obtaining the graft, laparotomy was performed, the common duct isolated, and a 3 cm. segment removed from its central portion (Fig. 1). The arterial graft was then sutured in place to the proximal and distal ends of the common duct utilizing an interrupted everting mattress stitch of 000000 black silk suture. This type of anastomosis prevented any tissue irregularity from projecting into the lumen and afforded good apposition between the transplant and the common duct. The lumens of the common duct and the femoral arterial segments corresponded fairly well, the usual internal diameter being 4 to 5 mm. After the ends had been sutured, the clamps were removed, and the anastomoses inspected for leakage. Additional sutures were inserted as needed. A portion of the gastrohepatic omentum was sutured about the common duct and its graft. The area was drained by inserting a Penrose drain through a stab wound in the right upper quadrant of the abdomen.

TABLE I. FREE ARTERIAL AUTOGRAFTS TRANSPLANTED INTO THE COMMON BILE DUCT

DOG NUMBER	LENGTH OF SURVIVAL (DAYS)	CAUSE OF DEATH	FATE OF GRAFT	DEGREE OF JAUNDICE
52	67	Sacrificed	Nonviable; stenosed	Marked
54	30	Peritonitis	Viable; leaked proximally	Marked
61	14	Peritonitis	Viable; leaked proximally	Marked
62	39	Peritonitis	Nonviable; stenosed	Marked
63	18	Unknown	Viable; graft intact	Slight
66	28	Hepatitis and cholangitis	Nonviable; stenosed	Marked

This procedure was carried out in six dogs (Table I) with survival from fourteen to sixty-seven days after operation. Two of the animals died with peritonitis secondary to leakage at the grafted site from necrosis of the transplanted arterial segment. Three of the dogs succumbed from stenosis and contracture of the graft. One animal was sacrificed at sixty-seven days postoperatively and the graft was found contracted markedly. In all six there was slight to marked jaundice with icterus varying from 20 to 80 units. In three animals the graft appeared viable and in three nonviable, without apparent relationship to whether stenosis or leakage had occurred.

Fig. 1.—Exposed common duct and operative field ready for introduction of arterial graft.

From these results it was believed that some of the failures were due to lack of support of the arterial segment between ends of the common bile duct. Thus, fibrosis and stenosis could develop before sufficient healing had occurred to allow for a patent channel. Accordingly a second series of animals was operated upon; in this series similar technique was employed except that a No. 9 French soft rubber catheter was used as a splint (Figs. 2 and 3). Additional holes were cut in the catheter to provide for passage of bile into the

duodenum. The catheter was inserted through the distal portion of the common duct into the duodenum, the arterial autograft was threaded onto it, and the tip of the catheter was placed into the proximal part of the common duct (toward the liver). The opposite end of the catheter was brought through the anterior wall of the duodenum, using the Witzel technique, and through a stab wound in the upper right quadrant of the abdomen.

Fig. 2.

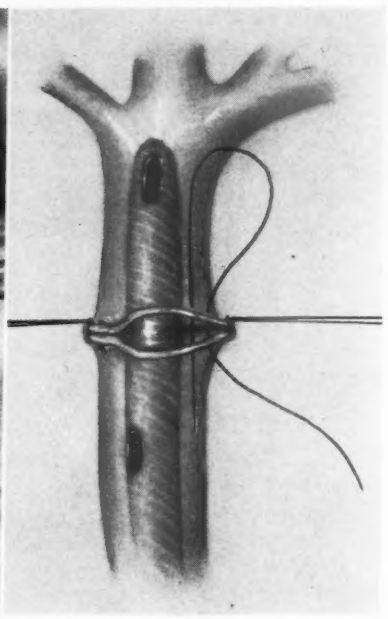

Fig. 3.

Fig. 2.—Arterial graft sutured in place in the extrahepatic biliary system over a rubber catheter for support.

Fig. 3.—Method of suturing free arterial graft into common duct defect with interrupted mattress everting sutures.

Nine dogs constituted this series (Table II). Four dogs died in postoperative periods varying from thirty to forty-seven days, and five were sacrificed at intervals after operation from fifty-four to sixty-two days. The catheter was passed spontaneously between six and twenty-eight days postoperatively. In only one animal (sacrificed at fifty-four days) was there evidence of patency of the arterial graft. All others exhibited stenosis with or without leakage and peritonitis. All except one dog showed obstructive jaundice.

From these results it may be concluded that the ancillary use of a catheter to support the arterial graft until healing occurred was without appreciable benefit.

In the final series of six dogs (Table III), the technique consisted of suturing an epidermal tube, with the epidermal surface inward, into a 3 cm. defect of the common bile duct. The graft was taken from the abdomen or the flank, and was 0.012 to 0.015 inch thick. Each tube of skin was scaffolded

by a No. 9 French catheter in the same fashion as in the preceding experiment. Five animals died with peritonitis in postoperative periods varying from twenty-six to fifty days. One was sacrificed at twenty-seven days and the graft was found to be stenosed at the end nearest the duodenum.

TABLE II. FREE ARTERIAL AUTOGRAFTS TRANSPLANTED INTO COMMON BILE DUCT WITH CATHETER "SPLINT"

DOG NUMBER	LENGTH OF SURVIVAL (DAYS)	CAUSE OF DEATH	FATE OF GRAFT	CATHETER PASSED (DAYS)	DEGREE OF JAUNDICE
5	54	Sacrificed	Viable; slight stenosis proximally	21	None
31	62	Sacrificed	Nonviable; stenosed	28	Marked
32	30	Peritonitis	Nonviable; leaked proximally	6	Marked
41	57	Sacrificed	Nonviable; stenosis	7	Marked
51	30	Hepatitis and cholangitis	Nonviable; stenosis proximally	21	Marked
55	60	Sacrificed	Nonviable; stenosis	21	Marked
71	58	Sacrificed	Nonviable; stenosis	14	Marked
73	36	Peritonitis	Nonviable; leaked proximally	21	Marked
75	47	Unknown	Nonviable; stenosed proximally	7	Marked

TABLE III. SPLIT-THICKNESS SKIN GRAFTS TRANSPLANTED INTO THE COMMON BILE DUCT

DOG NUMBER	LENGTH OF SURVIVAL (DAYS)	CAUSE OF DEATH	FATE OF GRAFT	THICKNESS OF GRAFT (INCHES)	SITE
28	34	Peritonitis	Viable; leaked proximally	0.015	Abdomen
30	50	Peritonitis	Nonviable; leaked proximally	0.015	Flank
73	26	Hepatitis and cholangitis	Nonviable; stenosed	0.012	Abdomen
74	30	Peritonitis	Nonviable; leaked proximally	0.012	Flank
97	45	Peritonitis	Nonvitable; leaked distally	0.015	Flank
98	27	Sacrificed	Viable; stenosed	0.012	Abdomen

These three series of experiments indicate that free arterial and split-thickness epidermal autografts are not successful for experimental transplantation into the biliary tract. This is probably due to the lack of vascularity to the graft and the irritating and deleterious effects of bile. It also supports the clinical observation that pressure within the biliary system is not sufficient to overcome the fibrosis of healing and prevent obstructive jaundice.[24]

CONCLUSIONS

1. Free arterial autografts were sutured into defects of the common bile duct in fifteen dogs (six without and nine with support of a rubber catheter). In all except one there was leakage and/or stenosis in postoperative periods varying from fourteen to sixty-seven days.

2. In six dogs an epidermal tube of split-thickness abdominal or flank skin was placed over a catheter and sutured into a defect of the common bile duct. In all animals leakage and/or stenosis occurred.

3. These experiments indicate that free arterial and split-thickness epidermal grafts are not suitable for bridging defects of the common bile duct in dogs.

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PRIMARY END-TO-END ANASTOMOSIS FOR CONGENITAL ATRESIA OF THE SMALL BOWEL

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THE surgical treatment of congenital intestinal atresia is still fraught with difficulty and hazards. Individuals with atresia of the intestinal tract will die if left untreated; rarely do the infants survive for more than one week without surgical relief.[1] When surgical intervention is attempted, the small lumen of the bowel, into which fluid from the proximal portions of the intestine has never made its entry, presents an exceedingly difficult technical problem. The performance of an intestinal anastomosis on such a bowel, with preservation of an intestinal lumen, frequently appears to be an impossible task.

There is no question that with the institution of better preoperative measures, and the use of antibiotics, more and more infants will survive. However, we should like to present a small operative modification that may aid in the more rapid functional recovery of the infants operated upon.

CASE REPORT

D. W. (Ancker Hospital No. 171814), a baby girl, was delivered normally on Oct. 4, 1950. She weighed 4 pounds and therefore was considered premature and put in an incubator. About twelve hours later it was noted that she had passed a tiny amount of thin, grayish green stool, which was rather dry in consistency. At about the same time, vomiting began and the abdomen was noted to be quite distended. Rectal examination revealed no obstruction. Physical examination of the abdomen showed a tightly distended abdomen with hyperperistaltic rushes and tympany.

Roentgenologic examination of the abdomen was then made. Examination of the abdomen, including multiple projections and inverted projections, with a thermometer in the rectum demonstrated considerable distention of the stomach. There was moderate distention of the duodenum and one, or possibly two, loops of jejunum. There was some suggestion of a mass in the right lower quadrant of the abdomen. No definite evidence of large bowel gas was found. The findings suggested most likely a volvulus of the midgut or an atresia of the small bowel. It was possible that the two were associated.

Surgery was then decided upon. After sufficient preparation and the installation of nasal suction by means of a small urinary catheter, surgery was performed, approximately thirteen hours after delivery.

Operative Procedure.—The abdomen was entered through a transverse incision just below the umbilicus. Drop ether was used as the anesthetic. When the abdomen was entered some clear, yellowish fluid was found. Large loops of bowel measuring about 3 cm. were found. These loops led down to a blind sac, at which point there was discontinuity of the bowel. A tiny threadlike fibrous band about 3 cm. in length connected this bowel to the distal collapsed portion of the bowel, which was 3 mm. in diameter. It was esti-

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mated that the atretic area was either in the lower jejunum or upper ileum. Further exploration of the bowel showed no further atretic areas. The proximal blind end appeared infarcted and gangrenous.

The fluid and air in the proximal dilated segment were aspirated through a needle hole. The size of the bowel was thus reduced to about 2 cm. in diameter. The blind pouch still appeared gangrenous, however, and it was thought best to resect it. About 8 cm. were therefore resected, down to the atretic fibrous band and up to the normal-looking bowel. A Potts vascular clamp with fine teeth was placed on this segment; a small rubber shod intestinal clamp having been placed some distance back. The Potts clamp was placed from the antimesenteric border, extending about 1 mm. beyond the uncut mesenteric edge.

Using the maneuver suggested by Wangensteen,[2] the distal collapsed bowel was then distended with air by means of a syringe and needle. This increased the diameter of the bowel to about 6 mm. A second Potts vascular clamp was then placed in an oblique manner from the mesenteric border through a small opening made in the mesentery. The clamp was so placed that the diameter of the bowel included within the blades was equal to that of the distended bowel above. When we were satisfied that both diameters were equal, the mesentery of the undistended bowel was then cleaned and removed as was the fibrous atretic area, and about 2 cm. of the unobstructed distal bowel. About 1 mm. of cleared bowel remained between the clamp and the mesenteric edge. The anastomosis clamps were then laid side by side, thus bringing the bowel ends together with one end rotated 180 degrees with respect to the other. Fine 000000 arterial silk was then used to perform the anastomosis. One layer of interrupted Lembert sutures was used throughout. About five sutures were used posteriorly and a similar number anteriorly. Special effort was made to keep the sutures very close to the clamps. After packing the area off, the clamps were then removed. A small amount of leakage from the proximal loop occurred. This was controlled easily by two extra sutures posteriorly, and two anteriorly. At the conclusion of the anastomosis, its patency was established by pushing air and fluid through from the proximal loop. The mesenteric defect was then closed, and the abdomen closed with silk (Fig. 1.).

Postoperatively, the patient did very well. Normal stools were passed on the first postoperative day. On the third day about 5 c.c. of Lipiodol were inserted through the nasal catheter; this passed normally through the bowel. On the fourth day the catheter was removed and a gradual feeding regimen was begun. Except for one bout of diarrhea in the very early postoperative period, the youngster has done remarkably well. On March 22, 1951, she weighed fifteen pounds and was on a normal feeding regimen.

DISCUSSION

The side-to-side intestinal anastomosis has been suggested as the only method that can be used for the re-establishment of continuity in cases of intestinal atresia in the jejunum of ileum.[1] However, it is well known that lateral anastomoses are not without their disadvantages. Pouches of the blind end of the afferent loop, ulcers within this segment, anemia, nausea and vomiting, distention, diarrhea, and nutritional disturbances have all been ascribed to lateral anastomoses.[3]

The great disparity in the size of the loops which are anastomosed has been the main reason for not performing end-to-end anastomosis. At the University of Minnesota Hospitals, it has been common practice to perform an end-to-end anastomosis at the time of the primary intestinal resection. A one-row layer of fine-silk Lembert sutures is sufficient. When disparity exists between two loops of bowel, such as in resection for acute intestinal obstruction,

an oblique end-to-end anastomosis is performed, rotating the bowel so as to avoid both kinking and a mesenteric angle. Experimental work in the laboratory has shown that the lumen so obtained is most adequate functionally.[4]

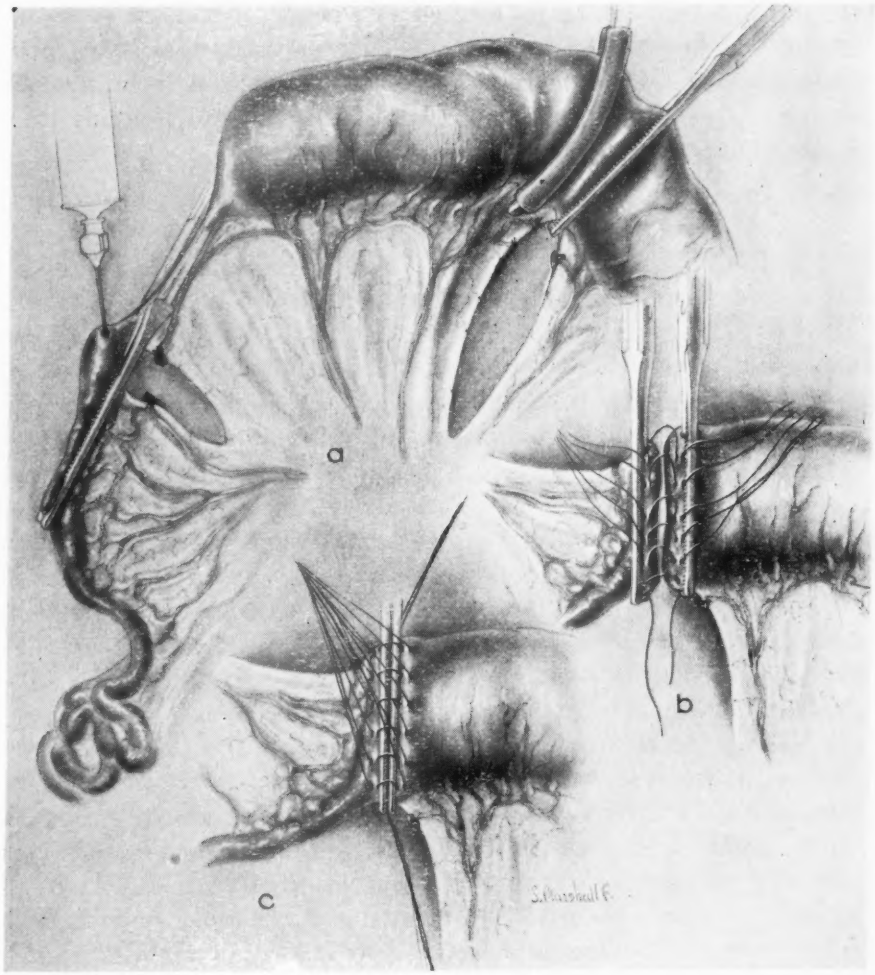

Fig. 1, *a*.—Placement of Potts vascular clamps on segments of bowel above and below atretic area. The clamps are placed in an oblique manner, from the antimesenteric border on the distended bowel, and the antimesenteric border on the undistended bowel. Previous to the placement of the clamp on the intestine below the atretic area, the bowel is dilated with air by means of a syringe. *b*.—Placement of 000000 silk sutures as the posterior row following resection of required segments of bowel. Special effort is made to keep the sutures close to the clamps. *c*.—Placement of the anterior row of silk sutures. Following this the clamps are removed and the sutures tied.

The use of the Potts fine-toothed vascular clamp, in the case presented, was most helpful in the performance of the anastomosis. This clamp allowed for little inversion, and a crushed cuff was not present. Arterial silk aided considerably in the performance of the anastomosis, especially when the distal segment was being entered with the needle. It was easily drawn through the thin bowel without damage to the wall. Finally, the use of the Wangensteen maneuver of distending the distal loop with air helped considerably.

SUMMARY AND CONCLUSIONS

1. A case of ileal atresia in a premature infant is presented.

2. Complete recovery followed resection and end-to-end anastomosis.

3. It is suggested that end-to-end, rather than lateral anastomosis in infants with intestinal atresia be performed as a more physiologic procedure.

4. End-to-end anastomosis was performed between two loops of bowel with a tremendous disparity in size. The use of the oblique technique, arterial silk, vascular clamps with fine teeth, and the maneuver of distending the distal loop with air, aided the procedure immeasurably.

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THE EFFECT OF HYALURONIDASE AND PLASMA ADMINISTERED SUBCUTANEOUSLY TO BURNED RATS

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THE frequently encountered and often difficult problem of quickly establishing an intravenous needle in a small child who has been burned would be a major problem in a large disaster situation. Therefore, we were interested in investigating other ways of administering plasma and blood in order to combat the initial shock and later protein loss due to the burn. In children with dehydration due to diarrhea, Schwartzman and others report successful, and in some instances lifesaving, results from the subcutaneous injection of plasma and blood with hyaluronidase. Generally, there has been much enthusiasm and optimism with regard to the possibilities of this mode of administration. Before recommending its use we wished to evaluate experimentally its effect in the burned animal.

Burn studies have emphasized the expansion of the body water available for the solution of extracellular ions and the shift of plasma protein from the intravascular to the extravascular compartment as a result of capillary damage. The redistribution occurs not only between plasma and the interstitial fluid of the burned area, and between burned cells and their immediate fluid environment, but also presumably in the undamaged areas of the body.

On the basis of our present knowledge of burn pathology and the shifts of osmotic equilibrium we would assume that the administration of plasma subcutaneously might possibly aggravate the intravascular hemoconcentration. Danowski has demonstrated that the "subcutaneous administration of a glucose or hypertonic electrolyte solution can precipitate shock in individuals who have already some measure of salt depletion as a consequence of their illness and in those who are in circulatory collapse because of trauma, burns, etc." Even a relatively small loss of extracellular electrolyte may plunge such a patient into manifest shock.

Blood serum differs from the interstitial fluid only slightly in electrolytic content but has a higher protein content. In the normal or dehydrated individual receiving this physiologic solution concomitantly with hyaluronidase which facilitates its absorption, no electrolytic disturbance has been noted. The protein factor, therefore, may be responsible for any fluid redistribution in an injured individual. The possibility of inhibition of the "spreading factor" is of prime importance. However, consideration should also be given to alteration of the effective activity of hyaluronidase in the animal under

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stress conditions. Seifter and co-workers have shown that the spreading factor of hyaluronidase is decreased in animals subjected to stress conditions. It is decreased equally by the administration of ACTH and to a lesser degree by adrenal cortical extract; conversely, in the adrenalectomized animal the hyaluronidase spreading factor is increased. Glick and Kaufmann have demonstrated that in vitro neither ACTH nor adrenal cortical steroids are inhibitors of hyaluronidase. These findings suggest that the inhibitory effect in vivo may be the result of the influence of ACTH and adrenal cortical extract on a physiologic mechanism. ACTH and the adrenal cortical inhibitors have been demonstrated by Glick and Kaufmann to elevate the level of the nonspecific inhibitor in the blood serum.

We present the following experiments as preliminary studies in this investigation.

EXPERIMENTAL DATA

Because of certain laboratory limitations we were forced to use the rat as the experimental animal. We intend to measure plasma protein, hematocrit, circulating blood volume, and coagulation time in further studies to be undertaken on larger animals. We elected in our preliminary study to compare hemoglobin determinations as an indication of hemoconcentration despite the limitations of this method as a measurement of hemoconcentration. In the burned animal, blood is destroyed and possibly the figures should be revised upward. There is also a hemoglobinemia, but since the control animals received equal burns this factor was eliminated.

METHODS

Thirty white male rats of the Evans strain and of approximately the same age and weight were used in this study. These were divided into series of six for statistical purposes. The animals were bled from the tail and checked by a simultaneous sample taken by a second individual. The lumetron photoelectric colorimetric method was used, and the optical density scale readings recorded. The tubes and pipettes were calibrated prior to undertaking the study. Determinations were not accepted unless two simultaneous determinations checked within the error of the instrument (.10). Rats were bled from the heart to obtain plasma.

The rat plasma was prepared in the usual manner of blood bank plasma. Ten cubic centimeters of whole blood were added to 2 c.c. of the anticoagulant ACD* solution. The mixture was then centrifuged and the plasma aspirated. The solution had a pH of 7.26.

Each rat was given 0.3 mg. Nembutal per 100 grams weight, subcutaneously. The hemoglobin was measured in six rats and the readings were compared with readings taken six hours later. During this period the animals received no food or fluid. They were then returned to the cages for several days and the hemoglobin again determined. This group of six were added to six other rats in which base hemoglobin readings were determined. Each of these twelve ani-

*Dextrose U.S.P. 2.45 Gm., Sodium citrate 2.20 Gm., Citric acid .80 Gm.

mals then received a third degree burn of approximately 15 per cent of their body surface by the application of live steam for two minutes to its right foot, leg, outer thigh, and side. Six of the animals received no therapy and a second hemoglobin determination was made at the end of the six-hour period. The other six received 2 c.c. of rat plasma per 100 grams of body weight every hour until each rat had been given three injections. Three of these animals also received hyaluronidase,* four units per injection of plasma. The hyaluronidase was diluted to 0.4 c.c. with distilled water and then added to the syringe containing the plasma and mixed. At the end of the six-hour period hemoglobin determinations were also made on these six. At a later date this procedure was repeated on a second series of twelve so that a total of eleven animals (one ceased respiration during the burning procedure and could not be used) were burned and received no treatment, six were burned and received subcutaneous rat plasma, and six were burned and received subcutaneous rat plasma and hyaluronidase. An additional six animals were burned and received human plasma, 2 c.c. per 100 grams body weight.

As a further check on the absorption of the injected fluids, 0.2 c.c. of phenolsulfonphthalein was administered with the first injection of rat plasma in both series and the urine of the animals receiving plasma tested with sodium hydroxide. At the time of the infliction of the burn the animals were in a reactive state and struggled.

TABLE I. INFLUENCE OF PLASMA AND HYALURONIDASE ON HEMOCONCENTRATION IN BURNED RATS

EXPERIMENTAL CONDITIONS	NO. OF RATS	CHANGES IN Hb IN SIX HOURS OVER BASE VALUE (PER CENT)
Unburned rats on cool day	6	-3 ±1.5
Unburned rats on warm day	6	1 ±1.3
Burned rats receiving no therapy	11	10 ±0.8
Burned rats receiving human plasma subcutaneously	6	15.5 ±1.4
Burned rats receiving rat plasma subcutaneously	6	12.3 ±1.8
Burned rats receiving rat plasma and hyaluronidase subcutaneously	6	15.5 ±1.9

SUMMARY

The results of these experiments were as follows.

1. There was no significant variation in the checked base hemoglobin in the same animals on different days.

2. There was no significant variation in the checked base hemoglobin in the animals kept for six hours without food or water. There was a slight increase on warm days.

3. Following the burn the control animals showed an average hemoglobin increase of 10 per cent ±0.8 at the end of the six-hour period.

*Alidase, G. D. Searle & Co., Chicago (500 units per vial).

4. The animals receiving human plasma showed an average hemoglobin increase of 15.5 per cent ±1.4.

5. Those receiving rat plasma had an average increase of 12.3 per cent ±1.8 for the same period of time. While this later alteration is not of sufficient magnitude to be statistically significant, we feel that the consistency of this variation is suggestive.

6. The rats receiving rat plasma and hyaluronidase subcutaneously showed an average increase of 15.5 per cent ±1.9. This is 2.7 times the standard deviation of mean using the formula $\sqrt{d^2_1 + d^2_2}$ which gives the joint standard deviation of the mean.

7. The urine specimens voided in the first hour after the concomitant subcutaneous injection of phenolsulfonphthalein were positive for phenolsulfonphthalein when tested with sodium hydroxide. This fact suggests that the fluid exchange is not completely unidirectional.

8. Clinically, the controls appeared more alert but had more severe hemoglobinuria. In the animals autopsied at the end of the six-hour period there were no large pools of plasma apparent.

CONCLUSIONS

Our data would indicate that the subcutaneous administration of plasma with or without hyaluronidase is of no value in the treatment of the burned animal in the acute phase, and suggest that such a procedure may even be dangerous and contraindicated. After the initial shock period, and period of fluid and electrolyte derangement, hyaluronidase and the subcutaneous administration of plasma may have a place in the therapeutic plan of protein restoration. The status of the usefulness of the enzyme in this later period is not established. Schwartzman and Levbarg have stated that an individual must have at least a total blood protein of 5.5 per cent in order that this mode of administration may be effective. They have suggested that "alteration in intracellular structures plus intercellular changes" may hinder absorption with hyaluronidase. Further detailed studies on larger animals must be made to evaluate these factors. Inasmuch as the blood serum inhibitor of hyaluronidase has been demonstrated to be elevated under "stress conditions" or following the administration of ACTH, we think the effect of the enzyme given intravenously to the burned animal should also be evaluated.

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Case Reports

METASTASIZING STRUMA

Case Report

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THE following case is of interest because metastasizing struma is a comparatively infrequently reported disease and is somewhat of a medical curiosity. Large single metastases can occur. In this case the area of metastasis was large enough to destroy the hip joint, yet grossly the thyroid gland was not detected as being abnormal.

Cohnheim first drew attention to metastasizing colloid goiters in 1876. Since that time approximately 100 cases have been reported in the literature.

PATHOLOGY

Foot[8] stated: "To the naked eye, the metastatic foci look like thyroid tissue, and under the microscope, they prove to differ little from it; there is not the slightest indication they are neoplastic aside from the fact that they are circumscribed lesions composed of thyroid tissue which are completely foreign to the organ in which they are found."

Typically, these tumors produce pressure necrosis of the surrounding tissue. Microscopically, they contain well-formed acini, many of which contain colloid, with no evidence of malignant changes. We found this situation to exist in our case (Fig. 2), and Tucker[6] and Kaplan[1] reported similar observations in their cases. Kaplan reported the following sites of bony involvement in order of frequency: skull, sternum, spine, ribs, humerus, femur, and pelvis.

TREATMENT

The treatment of this disease depends on the location and extent of involvement. If the metastases are confined to the neck, a radical neck dissection should be carried out. This should be the type recommended by Martin and co-workers[15] where the sternocleidomastoid muscle and internal jugular vein are removed with the intervening lymph nodes.

If there are widespread metastases, the treatment is similar to other malignant tumors of the thyroid gland. This tumor is radiosensitive. It is possible to treat it with external radiation. A more practical way at present is by radioactive iodine. A tracer dose is first given to pick up areas of metastases. Larger therapeutic doses are then administered as necessary.

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CASE REPORT

L. L. (No. 489621), a 50-year-old white woman, was admitted to the hospital on Nov. 24, 1948, with complaints of inability to move the right leg without hip pain, and of a mass in the right hip. The first symptom appeared in 1941 shortly after an injury to the right hip received from a fall. At this time the patient complained of numbness in the right leg. In 1942 a severe, boring, nonradiating pain, accentuated on motion, developed in the right hip. This caused a progressive decrease in her activity until 1944, when she became bedfast. Although still maintaining motor control of this leg, she remained bedfast until the time of entry into our hospital. During the period of time between 1944 and 1948, treatment consisted of symptomatic relief and bed rest. In October, 1948, an aspiration biopsy was done; the report was adenocarcinoma. (In a subsequent restudy of the few cells obtained by aspiration, the pathologist reported them as compatible with the diagnosis of metastasizing struma.)

The past history was not remarkable except for a cholecystectomy and appendectomy performed in 1936. A systemic review was essentially negative and there had been no symptoms of hyperthyroidism at any time.

At physical examination the patient was found to be a thin, white woman who appeared chronically ill. The admission pulse was 80, respiratory rate 20, blood pressure 140/50, and the temperature was normal. The thyroid gland was not enlarged to palpation. There was a large, soft, pulsating mass in the region of the right hip and inguinal areas which had an auditory and palpable bruit. The mass measured approximately 10 cm. in diameter and encroached on the lumen of both the vagina and rectum. There were moderately severe mixed hemorrhoids. The muscles of the right hip and leg were atrophic, although the patient still had motor control. Any motion of the right leg caused excruciating pain. There was reduced sensation of the right leg, especially of the foot. There was no edema. The reflexes were still intact.

Admission laboratory studies were essentially negative except for moderate leucopenia. X-ray studies (Fig. 1) demonstrated an extensive destruction of the right innominate bone with protrusion of the femoral head into the pelvic cavity. This mass was associated with soft tissue which was somewhat larger than the destructive process in the bone. The bone destruction was of a pressure type. The destruction did not extend beyond the mid-portion of the pelvic body and did not involve the crest of the ilium or the sacrum. X-ray studies of the chest and dorsolumbar spine were negative for metastases. Decalcification of disuse was noted on roentgenogram of the right femur. An excretory urogram was reported as demonstrating a left ureteral stone near the bladder, bilateral nephrolithiasis, left hydronephrosis, and medial displacement of the bladder and right ureter by the tumor mass. Kidney function was fairly good bilaterally. Barium enema was negative except for displacement of the cecum and terminal ileum by the tumor. Catheterization of the anterior tibial artery was done Nov. 28, 1948, under x-ray. The catheter could not be passed beyond the inguinal ligament.

A temporary diagnosis of a primary lesion of the right side of the pelvis was made. It was decided that before definitive surgery could be attempted, the left ureteral stone would have to be removed. On Dec. 3, 1948, a left ureterolithotomy was performed without incident. On Dec. 4, 1948, the patient spiked a high temperature with cyanosis, tachycardia, and neutropenia. In spite of antibiotic and supportive therapy, the patient died Dec. 8, 1948.

It was possible to obtain only a limited autopsy. The tumor was found to consist of a well-encapsulated mass approximately 10 by 10 cm. in size lying retroperitoneally and causing pressure necrosis of the bone. Large portions of the ilium, head of the right femur, and part of the ischium had been eroded. The mass extended into the pelvis medial to the ischium, but did not extend below the inguinal ligament. There was a 4 cm. saclike structure at one side of the tumor which had a smooth lining and had the appearance of an arteriovenous aneurysm, although no connection with the vessel could be demonstrated. The external iliac artery passed over the tumor and was not adherent to it. The vein was not identified.

Fig. 1.—Roentgenogram showing destruction of right innominate bone. The femoral head is shown protruding into the pelvic cavity.

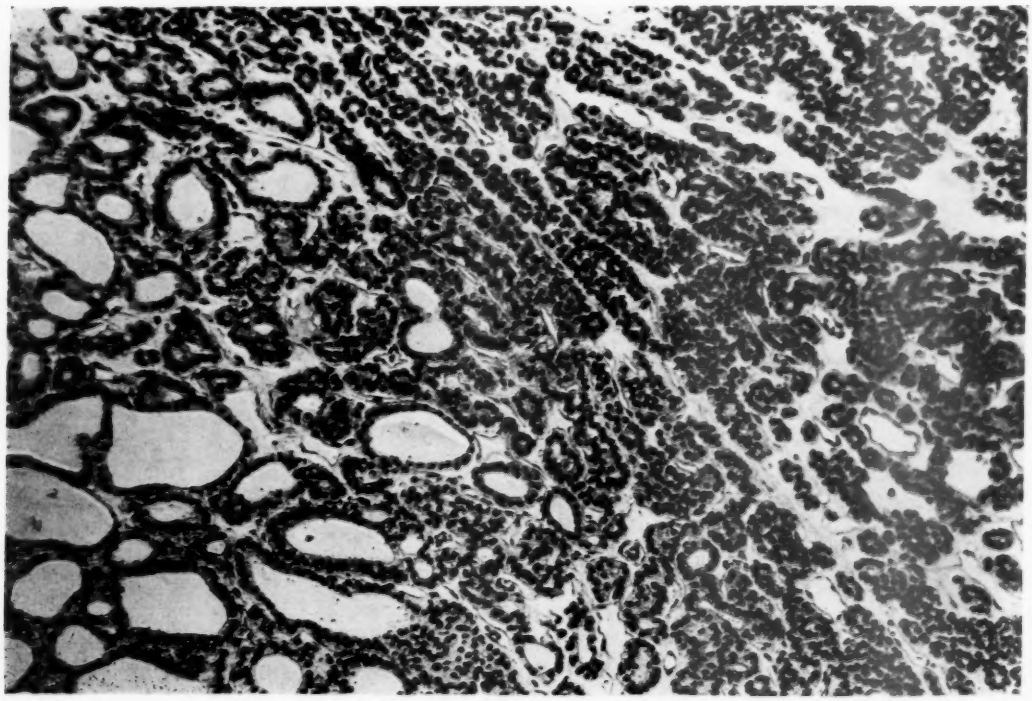

Fig. 2.—Photomicrograph of metastasizing struma removed from right pelvic area. Note the resemblance to thyroid tissue (×140).

On cut section, the tissue appeared friable, granular, reddish tan, and translucent with small hemorrhages. Under the microscope, the tumor was found to be composed of acini, many of which contained colloid (Fig. 2). No histologic evidence of malignancy was noted. The final pathologic diagnosis was metastasizing struma.

DISCUSSION

It is difficult to explain why it is possible to have a metastatic area as large as it was in this case without other areas of evident metastases. The patient had had symptoms referable to the right hip for seven years, and the tumor had caused enough destruction (Fig. 1) of the acetabulum and ilium to permit the head of the femur to protrude into the pelvic cavity. Hemipelvectomy was being planned for this lesion because the preoperative diagnosis was not correct. Had we known that the process was metastasizing struma, we would have attempted some form of radiation therapy. It should be added, however, that it might have been necessary in any event to execute the surgical procedure planned since there had been so much destruction, and even had the tumor been sterilized by radiation, the defect would have remained and caused almost as much disability and pain. If the surgical procedure had been carried out and the correct diagnosis established, we would then have proceeded with a tracer dose of radioactive iodine. If no other metastatic areas were detected, the patient should then have had a thyroidectomy performed, either surgically or radiotherapeutically.

SUMMARY

1. This is a case of metastasizing struma of the thyroid with a solitary metastasis to the right hip.

2. A brief discussion of the pathology and treatment of metastasizing struma is also presented.

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CHRONIC GIANT RUGAL GASTRITIS TREATED BY TOTAL GASTRECTOMY

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THE purpose of this article is to report an unusual case of chronic gastritis with giant rugae formation treated successfully by a total gastrectomy. A review of the literature revealed only four[1-4] reported cases treated by gastrectomy. Bartlett and Adams[1] tabulated 45 cases of chronic hypertrophic gastritis from the literature in which the diagnosis was proved on pathologic study.

CASE REPORT

A 20-year-old white seaman was admitted to the hospital on Aug. 17, 1950, complaining of excessive fatigue and epigastric burning pain. This epigastric pain, which began two months prior to admission, was relieved by food for periods of two or three hours but recurred regularly. During the last three weeks before admission, however, the pain was almost constant. The patient experienced the sensation that the food he ate did not seem to pass into the stomach immediately, but was blocked as if by a shelf. One-half to one hour later a sudden release would allow food to pass into the stomach as if a trap had been opened. He also noted increasing fatigue, dyspnea, and a weight loss of twenty pounds. He occasionally felt nauseated and vomited. There was no history of melena, hematemesis, or coffee-ground vomitus.

Physical examination revealed a thin, pale, young adult white man who appeared chronically ill. On examination the following positive findings were noted: The lungs were normal to percussion and auscultation. The heart sounds were regular and no murmurs were found. The blood pressure was 110/70. The abdomen was scaphoid and without tenderness. The liver, spleen, and kidneys were not palpable. There was no Virchow's cervical node. There was an ill-defined, firm, but movable mass in the midepigastrium. The reflexes, superficial and deep, were equal and active. There was no adenopathy.

The laboratory findings were as follows: red blood cells 2,600,000; hemoglobin 10 Gm.; white blood cells 8,500 with neutrophils 63 per cent, lymphocytes 34 per cent, monocytes 3 per cent, platelet count 240,000. Gastric analysis was: fasting HCl zero; total acidity 40. After an alcohol test meal the free HCl was 35; total acidity 40. Urinalysis was normal. Bone marrow smear was reported as 25 per cent red blood cell precursors, other nucleated red blood cells 75 per cent.

Examination of the chest failed to show any significant abnormality. Gastrointestinal series revealed a markedly enlarged mucosal pattern. There appeared to be a separation of the gastric folds in the region of the cardia with constriction in the proximal one-third of the stomach. The duodenal cap was unusually large and the duodenal loop appeared to be larger than normal. Malignancy, especially of the lymphoma group, could not be ruled out.

Gastroscopy revealed a normal esophagus. In the region of the cardia a large friable mass was encountered. The examination was terminated without bleeding, and without a biopsy.

The opinions or assertions contained herein are the private ones of the writers and are not to be construed as official or reflecting the views of the Navy Department or naval service at large.

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Preoperatively the patient received four transfusions of whole blood totaling 2,000 c.c. He was placed on a bland diet with supplemental intravenous protein hydrolysates and vitamins. On Sept. 9, 1950, an exploratory laparotomy was done under intratracheal nitrous oxide-oxygen-ether anesthesia. Through a left upper paramedian incision the abdomen was opened. The liver, preaortic lymph nodes, spleen, and pelvis were normal to palpation. The stomach was grossly enlarged and thickened. On palpation, the wall of the stomach felt as if it contained a cluster of worms, "a caput Medusa." Two node biopsies from lymph glands in the omentum close to the greater curvature of the stomach

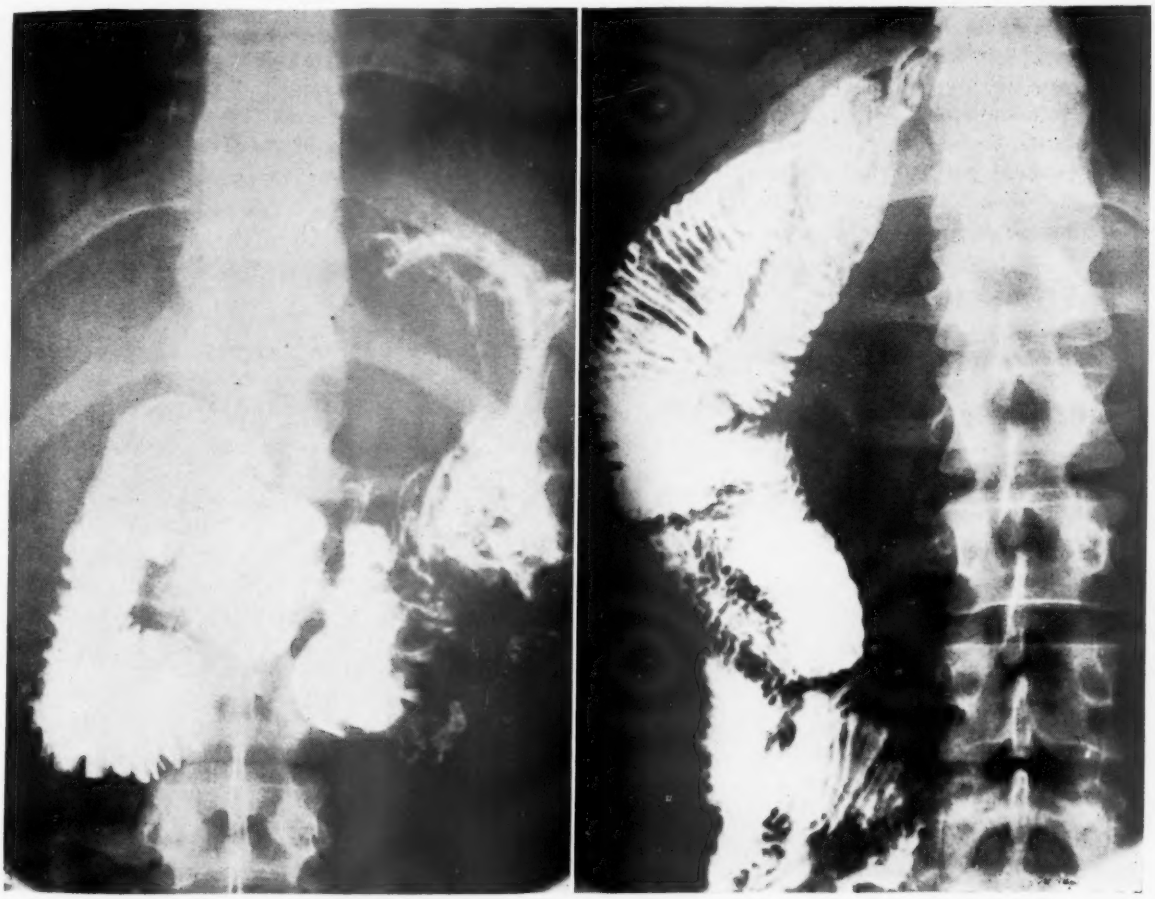

Fig. 1. Fig. 2.

Fig. 1.—Preoperative roentgenogram. (Official photograph, United States Navy.)
Fig. 2.—Postoperative roentgenogram. (Official photograph, United States Navy.)

were reported as showing simple hyperplasia. On the assumption that this was a resectable malignant lesion of the lymphoma type the incision was enlarged upward across the left costal cartilage, the seventh intercostal space, and into the pleural cavity, after notifying the anesthetist. A total gastrectomy was done after the techniques of Lahey.[6] It included en masse the omentum, spleen, stomach, and most of the gastrohepatic ligament. An esophagojejunostomy and a jejunojejunostomy was done and a Levine tube was passed through the distal loop of the jejunum. A Foley catheter was placed in the left pleural cavity for water seal drainage. Postoperatively the patient developed an atelectasis of the left lower lobe. Otherwise the convalescence was uneventful.

By Dec. 12, 1950, the patient had gained seven pounds in weight. He was eating six meals a day and his diet included meat, broiled fish, bland, soft fruits, and vegetables. During the postoperative period he received folic acid, 5 mg. twice daily, and liver extract twice weekly. On Dec. 22, 1950, a recheck barium meal failed to show evidence of pathology in the esophagus. There had been a complete gastrectomy with a subsequent esophagojejunostomy; both the afferent and efferent loops of the jejunum were well visualized and showed no abnormality. The side-to-side jejunostomy was demonstrated 20 cm. distal to the superior anastomosis. The jejunum showed a slightly coarser pattern but was otherwise normal. The five-hour film showed the barium in the terminal ileum.

By March 8, 1951, the patient had gained twelve pounds in weight. He was working as a clerical messenger. He ate three meals a day of slightly less than moderate portions with supplemental feeding in the midmorning, midafternoon, and at bedtime. The diet consisted of the usual foods, minus coarse vegetables, spicy foods, and foods high in fats. He complained of an occasional "water-brash" and had symptoms of the dumping syndrome immediately following heavy eating. He had not required dilute HCl for the occasional postprandial distress. In March the red blood count was 4,000,000, and hemoglobin 13 Gm.

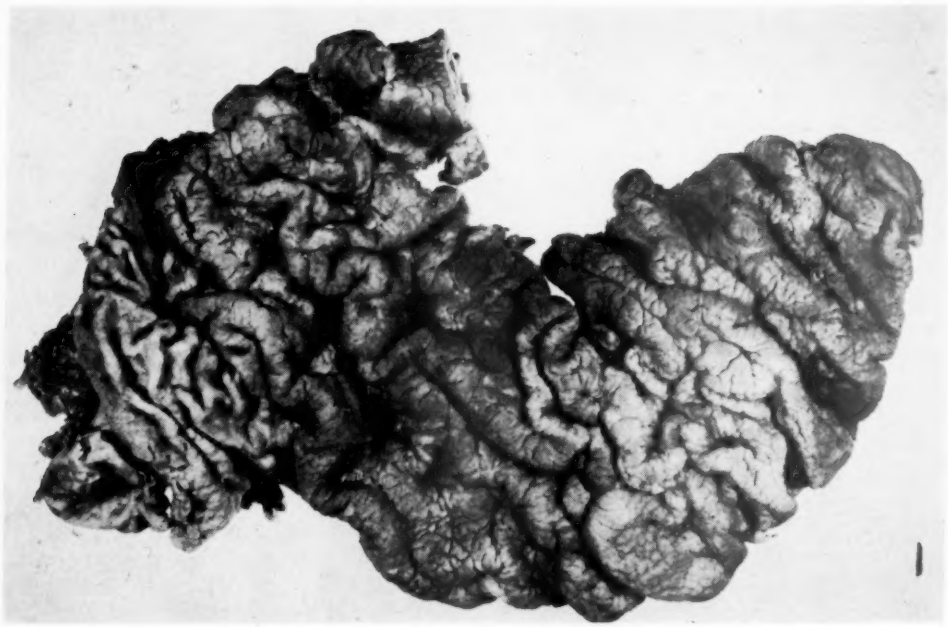

Fig. 3.—Gross pathologic specimen. (Official photograph, United States Navy.)

Pathologic Report.—The mucosa of the stomach revealed a rather dark mottling and was thrown into folds producing giant rugae, measuring 1.5 cm. in width and 1 cm. in elevation. These rugae were closely approximated, leaving narrow valleys between. The small slightly bulging gastric areas measuring 1 to 4 mm. in diameter were preserved throughout, giving a pebbled appearance to the surface which is in contradistinction to the smooth white surface seen in lymphosarcoma of the stomach. These rugae were of firm consistency and on cut section it is seen that the sharply demarcated mucosa constituted the bulk of the rugal masses. The glandular mucosa over the rugae average 5 mm. in thickness and the mucosa between the rugae average 4 mm. in thickness. On microscopic section it was seen that the submucosa was invaginated into the rugae forming a vascular connective tissue core which was everywhere surmounted by a well-defined muscularis mucosa. This connective tissue core was slightly constricted at the base of the rugae

giving the free end a somewhat clubbed appearance. The gastric pits were 1 mm. in depth and were lined by tall columnar mucus-secreting cells. The necks of the gastric glands were markedly elongated and the blind ends of these glands showed cystic dilatation, filled with an inflammatory exudate. There was a diffuse infiltration of the interstitial mucosal stroma with eosinophils, lymphocytes and plasma cells. There were less dense foci in the submucosal core. Pathologic diagnosis was gastritis; chronic, hypertrophic, with giant rugal formation.

Comment.—Gastritis is commonly divided into superficial, atrophic, hypertrophic and postoperative. The hypertrophic is the least common of the four varieties. In 1888 Menetrier described two types of hypertrophic gastritis, both of which he regarded as inflammatory in origin: the multiple discrete adenomas or "polyadenoma polypeux," and a diffuse mucosal hypertrophy, the "polyadenomas en nappe." This latter form may be localized as in the antrum, or be so extensive as to involve the whole stomach.

Discrete single or multiple polyps and polyposis are precancerous lesions, as are true adenomatous polyps elsewhere in the body. On microscopic section they show a connective tissue core which consists of the muscularis mucosa and submucosa. The glandular epithelium may be normal, with uniform polarity of cells and an orderly arrangement, or it may show varying degrees of metaplasia with loss of cell polarity, changes in the size and shape of the cells, and hyperchromatic nuclei. A change is regarded as "carcinoma in situ" if there occurs epithelial cell invasion of the connective tissue stalk. The diffuse mucosal hypertrophic gastritis or the "polyadenomas en nappe" does not have the appearance of true adenomatous polyps. It has no connective stalk and the muscularis mucosa and submucosa do not take part in the hyperplasia. The glandular structures become thickened, tortuous and branched. On microscopic study the zymogen cells, the acid-secreting cells and the chromaffine cells of the normal gastric mucosa are largely replaced by a mucus-secreting goblet cell that characterizes the intestinal mucosa. The mucosal infiltration of plasma cells, lymphocytes and eosinophils resembles a nonspecific inflammatory reaction, which as a rule does not extend into the submucosa. Grossly, the rugae of the stomach are prominent and have been described as resembling the convolutions of the cerebral cortex.

The present-day controversy is whether or not this type of gastritis is a precancerous lesion. Pathologically it may resemble a diffuse polyposis or a pseudo-polyposis or polypoid reaction of the mucosa of the stomach, not unlike that which occurs in chronic ulcerative colitis. Colcock[9] stated that the incidence of carcinoma developing in chronic ulcerative colitis is in direct proportion to the duration of the disease; that it varies from 5 to 8 per cent when the disease has been present for eight years.

It is because there is no general agreement as to the true nature of hypertrophic gastritis and its possible malignant degeneration, and further, because it may be extremely difficult to rule out an infiltrative gastric carcinoma or a lymphoma on clinical studies that surgical exploration is indicated. X-ray studies, gastroscopy, laboratory tests, the history and physical findings are unable at times to differentiate hypertrophic gastritis from a neoplasm. A biopsy

at operation is often indecisive as many pathologists are hesitant to state positively that a frozen section of a specimen is or is not a lymphosarcoma without a fixed stained slide for study.

The outstanding symptom of hypertrophic gastritis is epigastric distress not unlike the symptoms of peptic ulcer. There is an associated nausea, vomiting, and obstruction in lesions near the antrum or cardia. Benedict[8] lists epigastric pain as the outstanding symptom in 74 per cent of his cases, vomiting in 45 per cent of his cases and hemorrhage in 42 per cent. Anemia, weight loss, and malnutrition are common findings in hypertrophic gastritis. Schindler[7] reported a case of hypertrophic gastritis with death from cachexia treated conservatively on a diagnosis of carcinomatosis of unknown type and origin.

Many surgeons are of the opinion that a total gastrectomy is the operation of choice in hypertrophic gastritis; first, because of the difficulty which may be had to positively rule out an infiltrative carcinoma or lymphosarcoma; second, because of the marked cachexia, weight loss, anemia, and epigastric distress associated with the condition; third, because there is no agreement as to the true origin of hypertrophic gastritis—whether it is a benign hypertrophy and hyperplasia or a precancerous lesion.

SUMMARY

A case of hypertrophic gastritis with giant rugae which simulated a malignant lesion of the stomach is reported. There are only four cases of this type of gastritis treated by total gastrectomy reported in the literature.

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TORSION OF DYSGERMINOMA OF THE OVARY IN A CHILD

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OVARIAN neoplasms in infancy and childhood are uncommon. According to Schultz,[1] their incidence in girls less than 15 years of age is about 1 per cent of all tumors occurring in children of both sexes in this age group. A review of the literature by Costin and Kennedy[2] shows that of 200 ovarian tumors in infancy and childhood, approximately one-third were simple and multilocular cysts, one-fourth dermoid cysts, and slightly more than one-third either carcinomas or sarcomas. Since the recognition of granulosa-cell tumors and dysgerminomas is of relatively recent origin, they were apparently included in the group of sarcomas and carcinomas. Among ovarian tumors in infancy and childhood treated at the Mayo Clinic in twenty-eight years, there was only one dysgerminoma, forming 4.5 per cent of the entire series.[2]

This brief review illustrates the rarity of uncomplicated dysgerminoma in infancy and childhood, as compared with other types of tumors. A torsion of such neoplasm in a child makes the condition still more unusual. We were able to find in the literature[3, 4] only two reports of twisted dysgerminoma in children. Therefore, this report seems to be justified.

The term "dysgerminoma" was coined by Meyer,[5] who described this tumor and noticed that it corresponds to seminoma in man. He advanced the hypothesis that such heterotopic formations arise from cells present in primitive gonads of both male and female infants, and originate during a stage of evolution which precedes the differentiation of sex.[6]

Dysgerminomas occur with the greatest frequency in the second and third decades of life. They are encapsuled, have a rubbery consistency, are usually unilateral, and are formed by characteristic large cells with hyperchromatic nuclei, arranged in the form of alveoli. The tumors possess various degrees of malignancy and are highly radiosensitive.

In the early stages dysgerminomas produce the same symptoms as other pelvic neoplasms, namely tumefaction, pain, and symptoms of pressure on the bladder and on the rectum. The diagnosis has rarely, if ever, been made before the operation.

The treatment is surgical and should be followed by radiotherapy if there is evidence of invasion of the capsule.

For the sake of brevity, all nonessential findings are omitted from the case report:

CASE REPORT

K. Z., a white girl, 8 years old, had been in good health until two months prior to admission to St. Elizabeth Hospital, Jan. 30, 1951. At that time she began to complain of

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vague pain in the lower abdomen, especially on the left side, increased frequency of, and burning on, urination. The symptoms became more pronounced twenty-four hours before entry into the hospital.

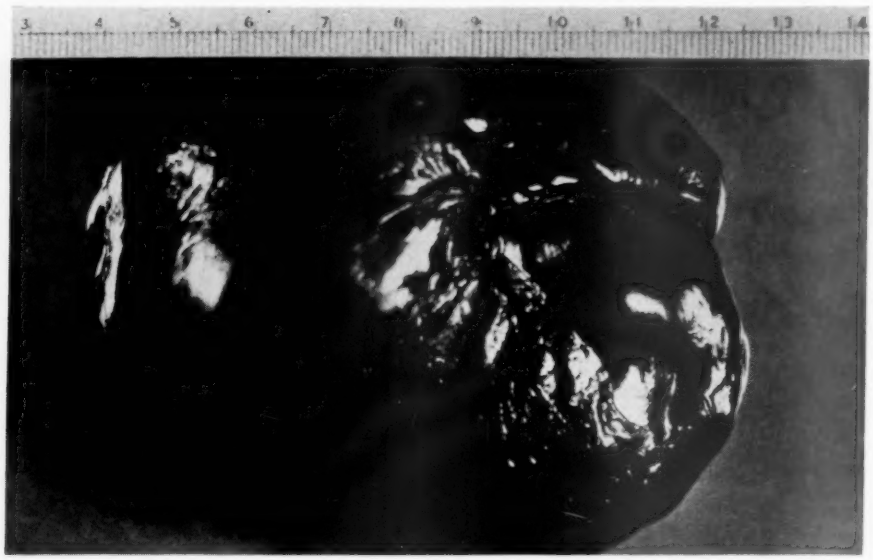

Fig. 1.—Gross specimen.

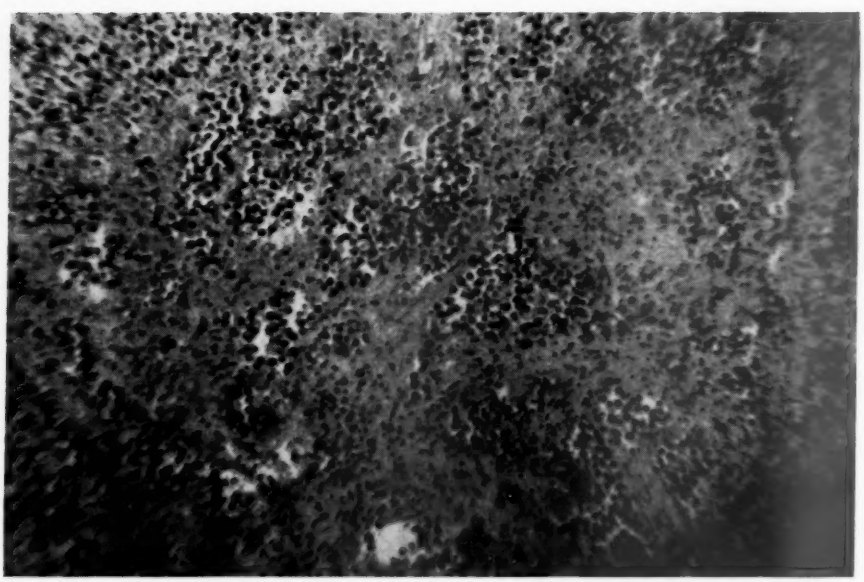

Fig. 2.—Microscopic view.

The family history was irrelevant and the past history and all physical and laboratory findings not mentioned here were noncontributory. Physical examination revealed a well-developed and well-nourished, acutely ill girl. There were no signs of hermaphroditism. The abdomen showed a slight distention and a moderate rigidity. On rectal examination a tender, immobile mass of a doughy consistency was found; it completely filled the posterior cul-de-sac. The uterus and the adnexa could not be clearly delineated. The temperature was

98.8° F., the pulse 100, and respiration 26. Laboratory studies showed a hemoglobin of 89.9 per cent; there were 4,580,000 erythrocytes and 8,700 leucocytes per cubic millimeter. The differential count was 76 polymorphonuclears, 21 lymphocytes, and 3 monocytes per 100 white cells. Results of urinalysis were within normal limits.

The examination of the urinary tract showed both kidneys to be of normal size and shape, and in the usual position. The renal function was normal. Descending urography visualized the calices and pelvis of each kidney; some blunting of the calices and a slight dilatation of the ureters were present. Both findings were more pronounced on the left side than on the right. The changes were compatible with a bilateral kidney infection. Antibiotics and sulfonamides were prescribed.

The day following admission the temperature rose to 101.4° F., the pulse rate was 120, respiration 24, and the blood count showed 19,500 leucocytes with 90 segmented, 6 lymphocytes, and 4 monocytes per 100 white blood corpuscles. The patient vomited some light yellow fluid, her pains became more intense and there was pronounced rigidity throughout the lower abdomen, associated with exquisite tenderness over the left lower quadrant.

The clinical impression was that of a perforated Meckel's diverticulum with a perimetritic abscess.

The abdomen was opened through a low midline incision. A globular tumor, of dark red color, with a smooth surface and a twisted pedicle, firmly attached to the left tube, was embedded in the posterior cul-de-sac. The capsule was intact, there was no ascites and no evidence of metastases. The uterus, both tubes, and the right ovary appeared normal. The tumor was excised together with the left tube. The patient recovered without complications.

The cut section showed the tumor to be soft but solid. The pathologic report* was as follows: The left Fallopian tube was thinly stretched over a firm mass which measured 8 by 12 by 10 cm. The fimbria of the Fallopian tube was free, and its lumen was patent. The Fallopian tube and the mass were discolored blue-red, and the mass had a firm consistency. Cut surfaces of the mass were moist, glistening, dusky red or mottled dark blue-red. The tumor mass weighed 130 Gm.

Microscopic examination revealed well-defined and/or ill-defined groups of cells containing varying amounts of acidophilic cytoplasm and large pale and/or darkly stained nuclei which formed columns, cords, and in places an alveolar arrangement. The stroma was ill defined, in places replaced by large areas of hemorrhage and necrosis, and elsewhere by edematous connective tissue cells which had lost their identity. Degenerative changes leading to cyst formation were present. Diagnosis was dysgerminoma of the ovary with hemorrhagic necrosis. Torsion of a solid tumor of the ovary.

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PERFORATED DUODENAL ULCER FOLLOWING BILATERAL THORACOLUMBAR SYMPATHECTOMY

A Case Report

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IT NOW seems well established that visceral sensation is carried by the autonomic nervous system, although the exact pathways have not been clearly determined for all abdominal viscera. At least a portion of these sensory fibers from the upper abdomen are carried through the splanchnic nerves. Clinical observations by Ray and Neill[1] and Bentley[2, 3] on visceral sensation before and after splanchnicectomy indicate that bilateral sympathectomy with section of both splanchnic systems may abolish visceral sensation in the upper abdomen. Effective relief of intractable pancreatic pain due to chronic pancreatitis, pancreatic calcinosis, or carcinoma can be obtained by bilateral splanchnicectomy. In addition to the alteration of pain response, preganglionic sympathetic denervation of the upper abdomen should theoretically produce alterations in the secretory and motor activity of the gastrointestinal tract, although Smithwick[6] has reported that alterations in motility are minimal under normal circumstances.

This raises several interesting speculations on the effect this procedure might have on the clinical manifestations of duodenal ulcer and its complications. Theoretically, at least, the unopposed vagal action might tend to increase the incidence and severity of ulcers in patients who have undergone bilateral sympathectomy for hypertension. Furthermore, the signs and symptoms of duodenal ulcer might be obscured when the normal pain response has been altered. Recently Craig, Morlock, and Hightower[4] reviewed 963 cases of sympathectomy with respect to the effect of this procedure upon gastrointestinal disease, specifically, duodenal ulcer. They reported twenty cases of duodenal ulcer, in one of which the first manifestation was acute perforation. Their studies would indicate that sympathectomy does not increase the incidence of, nor appreciably alter the clinical manifestations of duodenal ulcer. On the other hand, Smithwick[5] has reported cases of abdominal disease occurring in sympathectomized patients in which it was felt that the normal pain response was either abolished or altered. Although attention has been directed by previous writers to the potential difficulty of diagnosing abdominal disease in sympathectomized patients, few case reports are actually available. Since evaluation of this aspect of sympathectomy must depend on further clinical

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observation, the following case is considered noteworthy. This case is felt to represent an instance in which the diagnosis of perforated duodenal ulcer was delayed because the clinical picture was altered by bilateral thoracolumbar sympathectomy and splanchnicectomy which had been performed one month previously.

CASE REPORT

J. W., a 43-year-old white man, a machinist, was admitted to the hospital on May 26, 1950, with a history of angina and hypertension of approximately five years' duration. Following appropriate evaluation by the medical and surgical services, sympathectomy was recommended. This was performed in two stages, with section of the splanchnics bilaterally, and removal of the sympathetic chain on the left from T_1 through L_2 (the upper segments being removed because of left angina) and on the right from T_5 through L_2. The postoperative course was uncomplicated except for severe pain which the patient vaguely localized in the right lower chest and upper abdomen. This was attributed to the postoperative causalgia which is so frequently experienced by patients undergoing this procedure. He was discharged, symptomatically improved, on Aug. 8, 1950.

He returned to the hospital at midnight two days later complaining of severe right lower quadrant pain and vomiting. He had felt perfectly well until he ate his usual breakfast that morning and shortly thereafter he developed mild abdominal discomfort, became nauseated, and vomited. The pain became progressively worse, localizing in the right lower quadrant, and was described as constant rather than colicky in nature. No history of any previous gastrointestinal disturbance could be obtained.

Physical examination revealed an adult man of small stature who seemed quite apprehensive. Temperature was 97.8° F., pulse 92, blood pressure 130/90. The patient localized the pain quite specifically in the right lower quadrant a little above McBurney's point. Abdominal examination revealed no rigidity or tenderness until this specific area was touched. Even the lightest pressure on the abdominal wall at this point resulted in a violent reaction on the part of the patient. The skin of this area was hyperesthetic but the zone of hyperesthesia did not have a segmental distribution. Peristalsis was audible and interpreted as being normal in character. Rectal examination was negative.

A diagnosis of acute appendicitis was considered, but the peculiar sensitivity of the abdominal wall was so similar in many respects to the causalgic type of pain of which the patient had complained following the right sympathectomy that a period of overnight observation was elected in preference to immediate exploration.

Examination of the patient approximately six hours later revealed the same well-localized tenderness as noted previously. However, at this time there was definite rigidity in the right lower quadrant. There was no epigastric tenderness. Temperature was 98.6° F., pulse 100, white blood count 23,200 with 85 per cent neutrophils. Urinalysis was negative. A diagnosis of acute appendicitis was made and operation advised. At operation, fluid was noted in the right gutter. The appendix was normal. Further exploration revealed a free perforation of the duodenum which was closed without difficulty. The patient's postoperative course was uneventful. He was placed on routine ulcer management, including Banthine, and discharged from the hospital asymptomatic four weeks after closure of the ulcer.

Follow-up examination three months later revealed that the patient had no symptoms relating to the gastrointestinal tract. It is of interest to note that removal of the upper sympathetic chain on the left completely abolished the anginal attacks experienced preoperatively; however, the patient did describe discomfort at the root of the neck on effort, which was interpreted as an anginal equivalent.

Comment.—It is not unusual for acute perforation to be the first manifestation of duodenal ulcer. In the case outlined in this report the occurrence of perforation following sympathectomy may well have been purely coincidental,

a latent ulcer diathesis becoming manifest following the psychosomatic changes frequently seen in the postsympathectomy patient. However, the total absence of complaints usually associated with duodenal ulcer as well as the absence of any signs referable to the epigastrium when perforation did occur are worthy of comment.

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GALLSTONE OBSTRUCTION OF SMALL BOWEL OCCURRING IN THE ABSENCE OF THE GALL BLADDER

A Case Report

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ACUTE intestinal obstruction caused by gallstones has received considerable attention in the literature. This undoubtedly stems from the difficulty experienced in diagnosis plus the distressing mortality. Gallstones are one of the rarer causes of acute intestinal obstruction, being variously reported from 1 to 5 per cent.[1, 2, 3] Mortality figures range from 40 to 75 per cent.[1, 4]

The case presented is thought to be the first operative report of gallstone obstruction occurring in the absence of the gall bladder. The patient had undergone cholecystectomy two and one-half years previously. We can find only one other report[5] of a postcholecystectomy gallstone obstruction and in that case the diagnosis was made at autopsy.

CASE REPORT

A. S., a 67-year-old white man, entered the Colorado General Hospital on Sept. 29, 1950, complaining of unrelenting upper abdominal pain of twenty-four hours' duration. Past history revealed onset of peptic ulcer symptoms in 1936, manifested by burning epigastric pain exhibiting periodicity. Ingestion of food or alkali gave relief. The symptoms were fairly well held in abeyance with dietary management until 1945 when pyloric obstruction supervened. Subtotal gastrectomy with antecolic gastrojejunostomy was performed in 1945. A mild gall bladder attack was experienced in 1947. In April, 1948, the patient was first admitted to this hospital with a diagnosis of acute cholecystitis. Jaundice did not accompany either attack. Laparotomy disclosed acute suppurative cholecystitis with cholelithiasis, and cholecystectomy was performed. The disease was confirmed by pathologic examination. He was discharged on the tenth postoperative day.

The patient continued in good health until Sept. 28, 1950, when he was suddenly seized with a sharp, severe pain in the epigastrium while eating his noon meal. The pain became steady and progressively more severe and was accompanied by nausea, but not vomiting.

Physical examination revealed a very sick patient in obvious pain with rather marked dehydration. Temperature was 101° F. and pulse was 88. There was no evidence of jaundice. Abdominal examination disclosed exquisite epigastric tenderness with some rigidity. The tenderness extended along the right costal margin and right paracolic gutter. Rebound tenderness was present and was referred to the epigastrium and right side of the abdomen. Scout films of the abdomen failed to disclose free air or evidence of bowel distention. The white blood count was 23,300. Serum amylase was normal.

Our working diagnosis was peritonitis due to a perforated marginal ulcer. After careful consideration, we decided that emergency surgery would probably be of greater magnitude than the patient could withstand. Therapy consisted of continuous gastric suction, corrective intravenous therapy, antibiotics, and sedation. Improvement was rapid. Barium x-ray studies, however, failed to demonstrate a marginal ulcer. The patient was discharged after fifteen days' hospitalization to return at a future date for re-evaluation and possible vagus nerve section.

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The patient re-entered the hospital as an emergency admission on Nov. 3, 1950, with a history suggesting incomplete small bowel obstruction. Three days prior to admission he had experienced onset of mild, cramping, para-umbilical pain accompanied by nausea and several diarrheal stools. The diarrhea subsided and changed to obstipation. Persistent vomiting had occurred the night before admission and the pain had become more severe. Physical examination revealed a moderately ill patient in severe dehydration. Temperature was 97.8° F. and pulse was 84. The abdomen was slightly distended and peristalsis was visible. There were audible borborygmi accompanied by cramping para-umbilical pain. The abdomen was mildly tender throughout. The white blood count was 16,300. Roentgenograms of the abdomen suggested that the obstruction was in the distal small bowel. We thought the obstruction to be incomplete and most likely due to adhesions. We elected to initiate decompression with a Cantor tube and to correct the dehydration with intravenous fluids. The patient improved temporarily but then became worse and exploration of the abdomen was undertaken at once.

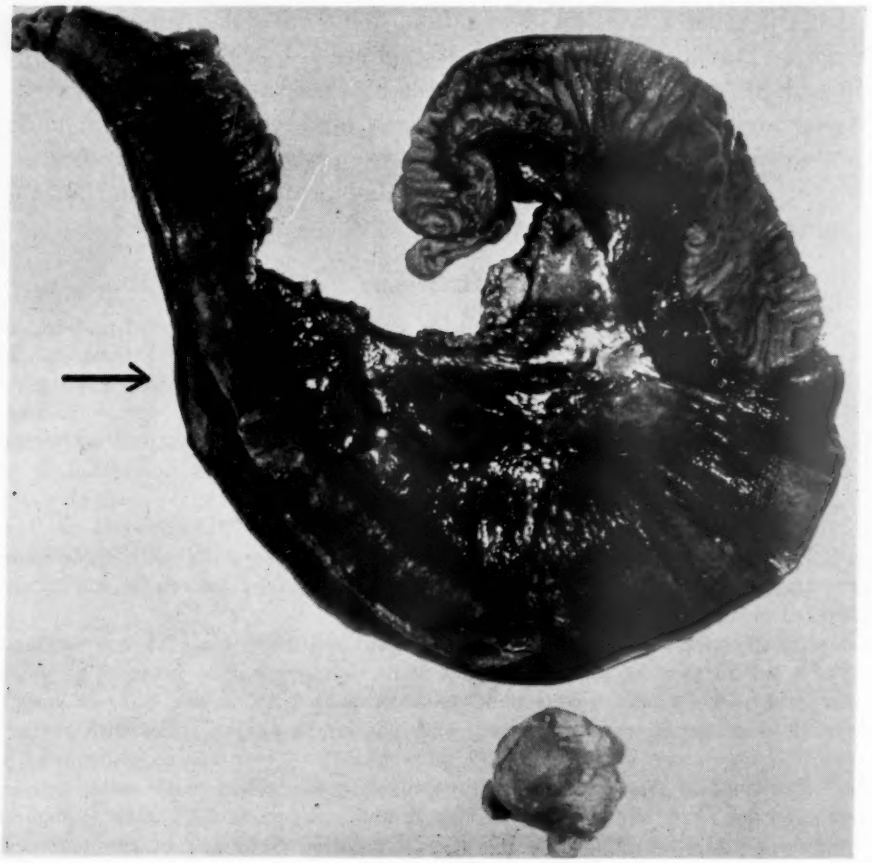

Fig. 1.—Resected segment of gangrenous ileum with arrow indicating point of obstruction of gallstone. The stone, shown at bottom of picture, measured 3 by 4 cm.

Laparotomy disclosed a large, firm, impacted concretion obstructing the bowel two and one-half feet proximal to the ileocecal valve. The bowel was nonviable for about 35 cm. proximal to the point of obstruction, and resection with end-to-end anastomosis was done.

Inspection of the antecolic gastrojejunostomy failed to demonstrate any pathology. However, there were numerous recent adhesions firmly adhering the proximal and distal limbs of the jejunal loop, suggesting the existence of an enteric fistula. The proximal limb was not unusually long. The gall bladder was absent and the common duct was not enlarged.

The patient's recovery was uncomplicated and he was discharged on his fifteenth postoperative day. The concretion measured 3 by 4 cm. and subsequent chemical analysis demonstrated it to be a biliary stone.

DISCUSSION

This patient had a subtotal gastrectomy for proved duodenal ulcer in 1945. He then underwent cholecystectomy in April, 1948, following his second attack of cholecystitis. Two and one-half years later he suffered acute intestinal obstruction due to a large gallstone.

What was the source of the biliary stone? A gallstone formed in the biliary tree may reach the intestinal tract in one of two ways. It may pass through the cystic and common ducts or it may reach the bowel through a cholecystenteric fistula. Moore,[6] in 1925, suggested that most gallstones capable of producing obstruction pass by the latter route. Other authors[1, 7] have confirmed this. In our case, no possibility of fistula existed since the gall bladder had been surgically removed, nor did the patient exhibit evidence of passage of a common duct stone. He was never jaundiced and the common duct was not enlarged.

We believe the only possible site of formation was the duodenum or proximal jejunal loop. Perhaps a small stone entered the duodenum from the common duct where it remained dormant for an unknown length of time, gradually increasing in size. The existing subtotal gastrectomy with functioning gastrojejunostomy might favor growth of the stone if the proximal stoma were small. The physiology of the first portion of the duodenum would tend to simulate that of the biliary passages in the absence of gastric contents. The stone did not show any apparent inclination to enter the stomach as one might expect. Perhaps this was due to a minimal contraction of the proximal jejunostomy stoma, the stoma being adequate to allow unobstructed passage of the liquid duodenal contents but too small to allow passage of the stone. This seems to us to most logically explain the source and growth of the stone to sufficient size to result in intestinal obstruction.

Another interesting feature of this case is related to the patient's hospitalization with the diagnosis of perforated marginal ulcer. In retrospect, we feel this diagnosis was in error. Visualization of the gastrojejunostomy failed to disclose evidence of either an active or a healed marginal ulcer. We did find evidence suggesting a healed enteric fistula between the proximal and distal limbs of the jejunostomy. The most reasonable assumption would seem to be that the stone eroded between the two limbs with some leakage of bowel contents, simulating the clinical picture of a perforated ulcer. Approximately a month then elapsed before the stone impacted in the lower ileum causing obstruction and gangrene.

This case might well have been listed as a recurrence of ulcer following subtotal resection. Perhaps it should still be considered as an unusual or unique complication of the gastric surgery.

SUMMARY

1. A case is presented of small bowel obstruction due to a large gallstone occurring in the absence of the gall bladder.

2. We believe that the biliary concretion must have formed in the duodenum.

3. Previous subtotal gastrectomy may have been the important contributing factor in the etiology.

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DESMOID TUMORS

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TUMORS of the desmoid type were first described morphologically by McFarlane in 1832. The term desmoid (meaning band appearance) was introduced into the literature by Muller in 1838, because he was impressed with the dense tendon-like consistency of the tumor.

Desmoid tumors are rare, as evidenced by their incidence of 0.03 per cent of admissions to Memorial Hospital of New York. They constituted 0.13 per cent of over 16,000 tumor cases from the records of Viennese hospitals.[1] There were only six cases in twelve years in the German Surgical Clinic in Prague.[2]

Many reasons for the presence of desmoid tumors have been advanced by different writers, but no definite causative factor could be determined. Trauma has been mentioned most frequently, but here again, no definite proof is available. Pregnancy seems to be etiologically significant, but not conclusive because a fairly good number of cases have been reported in men! Sonntag[3] made the significant statement that "87 per cent of the patients are female and of these 95 per cent have borne children." Pearman and Mayo[4] reported on seventy-seven cases of desmoid tumor diagnosed at the Mayo Clinic in thirty years, in which twenty-two (28 per cent) of the patients were men, and fifty-five (72 per cent) were women, with histories of pregnancy in thirty-three (60 per cent of the women). Pack and Ehrlich[1] stated, "With but one exception all the female patients in this series had a recent gestation."

These tumors may be found in any of the muscles of the abdominal wall, but are most frequent in the rectus muscles. They may, however, involve several muscles or, in rare cases, all the abdominal muscles are affected.[3] They have been described as, "An unencapsulated, infiltrating fibroma of fascial or aponeurotic origin with a microscopic appearance which varies from that of an acellular fibroma to that of a low-grade fibrosarcoma."[1] Desmoid tumors always invade, compress, and destroy muscle, while fibromas are not aggressive. Desmoids are deep-seated, while fibromas are subcutaneous, and desmoids tend to recur especially following limited surgical excision, while fibromas do not.

The usual clinical picture seen is a young woman who has borne children and presents herself with a firm, usually oval, circumscribed mass in the lower abdominal muscles. Usually pain is not particularly significant, nor is there great discomfort even where the tumor is of considerable size. The mass is usually slow-growing. Occasionally it is difficult to be certain whether the tumor is limited to the abdominal wall or is intra- or extraperitoneal. In these cases, surgical exploration must be resorted to, to establish its exact location. Diagnosis, however, is usually not difficult and is based on the

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previously mentioned typical findings. Aspiration biopsy is usually of little value in diagnosing a desmoid tumor because of the dense fibrous nature of this tumor. It can, however, be of value in ruling out such malignancies as liposarcoma, lymphosarcoma, or metastatic carcinoma. Primary radical excision might not be the treatment of choice in these cases, as it would be were the tumor a desmoid.

Fortunately, desmoid tumors are slow-growing, and not given to malignant transformation. Even should such transformation occur, desmoid tumors develop into low-grade fibrosarcomas which rarely involve the regional lymph nodes or produce distant metastases.[1] They do, however, have a strong tendency to recur and even become larger than the original growth. This is especially likely to happen during subsequent pregnancies and childbirths.

The treatment of choice is radical surgical excision which must be wide and complete, thereby reducing the likelihood of recurrence. Here one may encounter difficulties in repairing the resulting defect, especially following removal of large tumors. Radiation therapy has been used successfully, particularly in the so-called inoperable cases and in cases with extensive recurrence.

CASE REPORT

V. K., a 22-year-old (1950) married Negro woman, para ii, gravida ii (1950), was first admitted to St. Peter's General Hospital (44021), Aug. 8, 1944, because of pain in the lower left quadrant and umbilical region for the preceding four weeks. Examination revealed a large mass extending throughout the abdomen with tenderness and crepitation in the left upper quadrant. A diagnosis of multilocular right ovarian cyst and chronic appendicitis was made. Operation confirmed these findings and a right salpingo-oophorectomy and appendectomy were done. The pathologist reported adenocarcinoma of the right Fallopian tube (the author, however, considers this doubtful), multilocular cyst of the right ovary, and chronic appendicitis. All other laboratory reports were within normal limits.

The patient was then delivered of a living male child on March 14, 1949, at Middlesex General Hospital (No. 37885). The pregnancy and labor were uneventful and the patient insisted that the mass in the abdominal wall, about to be described, was first noticed the day after her delivery! The attending physician did not recall noticing anything unusual about the abdomen during his very limited prenatal care.

The mass made its appearance in the lower angle, and to the left, of the incision scar. At first it was very slow-growing, but during the subsequent pregnancy it seemed to enlarge rather rapidly. The prenatal record has a notation on April 21, 1950, that there was a mass in the lower left quadrant approximately the size of an orange. It was thought to be a chondroma, but a roentgenogram taken on the same date failed to reveal anything other than the existing pregnancy of six and one-half months' duration. She was delivered uneventfully of a living female child on June 12, 1950, at St. Peter's General Hospital (No. K3185).

During all these months, aside from its increasing size and mechanical inconveniences, the patient had had no complaints directly attributable to the tumor mass. She was, however, advised to have it removed and presented herself on Aug. 14, 1950, for this purpose.

The patient had been seen at Surgical and Gynecological and Obstetrical conferences at St. Peter's General Hospital, and examined by a great many of the members of both staffs, with a variety of preoperative diagnoses. Our impression was that we were dealing with a fibrochondroma.

The patient was of slight build, weighing 95 pounds. The findings, except for the vagino-abdominal examination, were all essentially negative. There was a midline incision scar with keloid formation, particularly marked at the lower angle. To the left there was a dense, firm, globular mass about 12 cm. by 10 cm. by 8 cm. which seemed to arise from, and was firmly adherent to, the symphysis pubis. Its upper pole reached almost to the umbilicus and was slightly movable. (It gave one the impression of being extraperitoneal.) There was no tenderness or rigidity over this mass or elsewhere in the abdomen.

Fig. 1.—Photograph taken at operation.

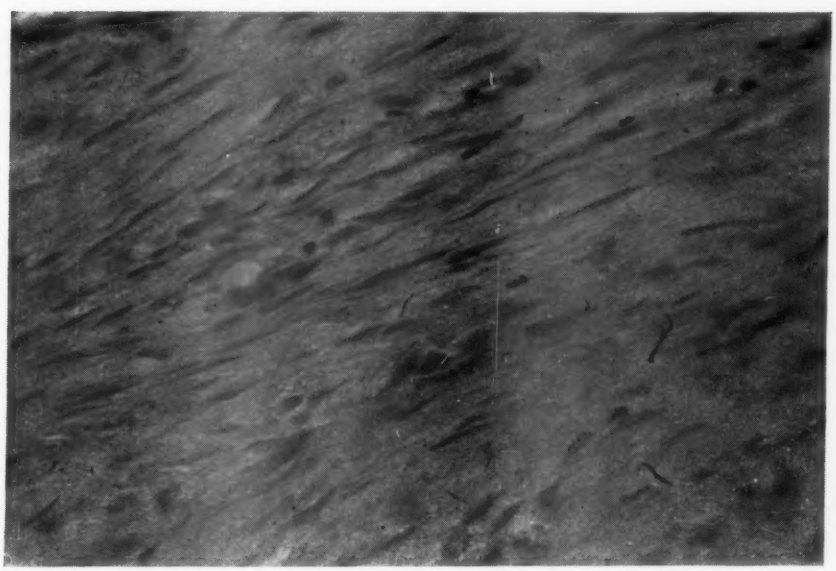

Fig. 2.—Low-power photomicrograph.

The introitus was multiparous, the perineum firm. The uterus was normal in size and shape and was in third degree retroversion, but readily replaceable and bore no relationship or connection to the abdominal mass. The cervix was clean. Both fornices were negative for tenderness or masses.

Operation.—The patient was operated upon Aug. 18, 1950. The previous incision scar was removed. A moderate amount of bleeding was encountered and a rather large, irregular, superficial tumor was then encountered mainly in the lower belly of the left rectus muscle. This tumor was carefully dissected out, which entailed at times severing of fibers of the rectus muscle, or separating them from the tumor and from their insertion into the symphysis pubis. The tumor was completely extraperitoneal and was removed with blunt and sharp dissection from its very close, intimate attachment to the periosteum of the symphysis. After removing the tumor, the lower belly of the rectus muscle was reconstructed by utilizing the cut fibers of the muscle and the fibers which were pushed away, suturing all these to each other and to the periosteum of the symphysis. The peritoneum was opened because of the retroversion of the uterus which was corrected by a typical Baldy-Webster suspension: the round ligaments were brought through the broad ligaments, sutured to the posterior surface of the uterus which was previously scarified, and to each other forming a complete satisfactory hammock support for the uterus. The right tube and ovary and appendix had been removed at the previous operation. The left tube and ovary were normal and were left in situ. The uterus appeared entirely normal. The abdomen was then closed in layers, the peritoneum with 00 chromic sutures. The fascia presented a difficult problem because of the defect produced by having removed the tumor with some of the fascia overlying it. This fascia was intimately adherent to the tumor and could not be dissected away. The fascia could be imbricated in some areas, but in the upper and middle regions a small defect had to be left because it could not be approximated without undue tension. No. 1 chromic interrupted sutures were used for this purpose. A continuous suture of 00 plain sutures was used to approximate the superficial fascia, after which the skin was approximated with dermal interrupted inverted mattress sutures. The patient's general condition at the end of the operation was good.

*Pathologic Report.**—

Gross: The specimen was a bulky tumor mass 9.5 by 7.5 by 5.5 cm. having a roughly pear-shaped contour and tapering to a point of attachment. Cut section revealed a brownish, somewhat translucent tissue not unlike muscle, which was infiltrated by broad and narrow strands of whitish scar tissue, involving about one-third its substance, extending in a radiating manner from the region of the pedicle into the more rounded body of the tumor.

Microscopic: Sections revealed masses of simple connective tissue of collagenous type showing considerable vascularity but of entirely mature character. The individual cells were well formed and the nuclei were elongated and of more or less uniform size and shape. The fibers formed long parallel rows and interlacing bundles and in a few areas showed hyalinization and loss of vascularity. Some of the fibers were very bulky and of keloidlike character.

Diagnosis.—Diagnosis was fibroma (''desmoid'') of the abdominal wall.

The patient made a smooth, uneventful recovery. She was hospitalized longer than usual because of the fascial defect and fear of lack of strength of the healing rectus muscle and sheath. She was discharged on Aug. 27, 1950, and seen on September 15 and December 11. On September 15 there was considerable induration present and a possible recurrence was feared; but re-examination on December 11 showed a minimal amount of induration with good healing.

This patient was last seen on June 4, 1951, at which time she was pregnant, her last menstrual period having been on Dec. 25, 1950. There were no evidences of recurrence at this time.

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Recent Advances in Surgery

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RECENT ADVANCES IN FROSTBITE

WITH PARTICULAR REFERENCE TO EXPERIMENTAL STUDIES CONCERNING FUNCTIONAL PATHOLOGY AND TREATMENT

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THE undertaking of another winter military campaign has once again brought the problem of frostbite to the fore, as such campaigns have done repeatedly in the past. Although frostbite has always occurred sporadically among the civilian population, it ordinarily occurs in great numbers only in time of war. This is understandable, since it is essentially a disorder of privation and hardship. Even in normal civilian populations accustomed to cold weather the incidence of frostbite is almost invariably greatest during the first day or so of a severe cold spell, indicating that adaptation of living habits and dress is all important in its prevention.[1] During wartime, such adjustments are frequently impossible because of the military situation and, in addition, warfare brings into play other factors thought probably, or possibly, to predispose to such injuries—immobility in cramped positions, lack of opportunity to change into dry clothing, fatigue, emotional tension, dietary inadequacy.[2]

The peaks of interest in frostbite have not, unfortunately, been ordinarily associated with similar spurts of investigative activity contributing to our understanding of this disorder and of its prevention and treatment. Indeed, the medical literature concerning this problem is not only relatively sparse, but much of it is speculative and unscientific. Undoubtedly this is in large measure the result of the difficulties inherent in the clinical study of this condition. The rarity of frostbite in the average civilian population generally precludes its study in numbers likely to yield reliable new knowledge. Though great numbers of cases have occurred in military campaigns, the exigencies of war, the necessity for speedy evacuation of the injured from one medical installation to another, the relatively scarcity of personnel trained and interested in clinical investigation, and the virtual impossibility of any individual or group following through any such casualties from the time of injury to final rehabilitation have rather effectively rendered this ample clinical material of little value in furthering the advance of our knowledge. Furthermore, the problem of studying frostbite in

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man is complicated by extraordinary difficulty in controlling the experimental observations. There is no way of predicting with accuracy the severity of the injury from the initial appearance of the lesion, and often even the conditions of exposure, such as temperature and duration, are unknown. It is as a consequence of such difficulties that it has been necessary to rely so heavily upon animal experimentation.

The experimental investigation of frostbite began seriously during World War II. As a result of these studies, even though our knowledge is still woefully inadequate, we are in a better position to treat the condition intelligently than at any other period in history. Before this time, except for the influence of a few accounts of personal experiences of military surgeons, such as Larrey,[3] treatment was a matter of folklore. The prevailing custom was to rub the frostbitten extremity with snow or to allow it to warm slowly in a cold room, retarding thawing with the aid of locally applied snow or ice. Such treatment was supported by numerous authors[1] with little or no scientific basis. Indeed, such practices have persisted up to the present[4] and, becaues of their deep-rooted origin, they will without doubt be difficult to displace for a long time to come.

This review of recent investigations into the functional pathology and treatment of experimental frostbite was undertaken with the hope that a study of the available evidence would lead to a better understanding of the condition, to a more rational approach to its treatment, and to a clearer delineation of needed future research. By frostbite we mean the condition resulting from exposure to cold of sufficient severity and duration to produce actual freezing to ice of the exposed tissues. The other cold injuries, such as trench foot and immersion foot and hand, have many features in common with frostbite, but there are also differences which justify their separate consideration. Our review will be concerned only with true frostbite.

PHYSIOLOGY AND PATHOLOGY

When an extremity is exposed to severe cold, vasoconstriction occurs.[5] Clinically this is usually evident as blanching of the skin. The skin may then become bright pink in color due to capillary dilatation and the failure of oxyhemoglobin dissociation at low temperatures. The capillaries, however, become contracted before freezing occurs.[6] According to Lewis,[5] the vasoconstrictor response to cold comprises three reactions. One is a local and persistent vasoconstriction which is due to the direct effect of the low temperature on the blood vessels. The second is a transient local reflex vasoconstriction mediated through the sympathetic nerves. The third is a generalized and persistent vasoconstrictor response consequent to the effect of the cooled blood upon the hypothalamic vasomotor center. Though the arterioles and small arteries are primarily involved, all components of the vascular tree are affected.[7, 8] Coincident muscular weakness and inactivity of the chilled extremity contribute further to the decrease in circulation. All these reactions undoubtedly tend to serve a useful function in aiding the conservation of heat, but in exposure to cold of sufficient severity and duration they jeopardize the exposed part by contributing to tissue

anoxia. An additional factor mitigating toward injury from anoxia is the failure of the blood to part with oxygen at low temperatures.[9] The protective mechanisms of supercooling[10] and of the response of the arteriovenous anastomoses[11] are ineffective in preventing freezing if the exposure is too intense and of too long duration.

When the physiologic defenses to cold are overwhelmed, freezing occurs The freezing point of skin has been placed between 0 and −2° C.[10]; as a matter of fact, frostbite rarely occurs except at considerably lower temperatures, because of the phenomenon of supercooling. When solidification does begin it progresses rapidly to involve all of the supercooled tissue, which becomes white, opaque, and hard. Frozen tissue does not become brittle, however, until cooled to below −80° C.[12] During the period of freezing there is no blood flow through the frozen part and marked vasoconstriction proximal to it.[8]

The resultant injury suffered by tissues subjected to freezing varies directly with the extent and depth of the solidification which, at least up to the point at which all the exposed tissue is frozen, is dependent upon the severity and duration of the exposure.[13, 14] The actual damage inflicted may be considered as primary and secondary in nature. The first includes the direct cold injury to the cells during freezing and thawing, and the anoxic injury due to vasoconstriction before, during, and immediately after, solidification. There is considerable evidence suggesting that the duration of the frozen state per se is not of primary importance, particularly evidence derived from studies concerned with the preservation of single-celled organisms by freezing. The duration of freezing in the living mammal, however, is directly related to the extent of damage which may result; this relationship may be dependent, not upon the duration of the frozen state per se, but upon other associated factors such as the duration and extent of vasoconstriction, anoxia, and capillary stasis.[14] Except for those frozen cells which are thus killed outright, death of tissue, which is the gravest sequel to frostbite, occurs as a result of secondary changes following thawing.[15, 16]

After thawing there develops a reaction which is commonly referred to as reactive hyperemia. It certainly resembles the reactive hyperemia which follows arterial occlusion. Kreyberg[15] spoke of it as an aseptic inflammation in which the vascular component overshadows the cellular component of the reaction, although both are present. Lewis[9] likened it to the triple response reaction to histamine and suggested that it was caused by histamine-like substances liberated by cellular injury during freezing. There is reason to believe it may represent the reaction to slightly diffusible abnormal cell products resulting from direct cold injury or ischemic injury.[15] To be most effective, treatment should be instituted before or in the early stages of this phase of the cold injury.

When it is placed in a warmer environment, the frostbitten extremity thaws by conduction of heat from the surroundings and the adjacent portion of the body proximal to the frozen area. Thawing tends to occur first along the course of blood vessels. Grossly the skin may remain blanched for a variable period of time, following which it becomes red and warm and the pulses bounding. However, actual constriction of the arterial tree may persist for some time. Arteriographic studies indicate that the arterial tree is rarely completely

open during the period of so-called hyperemia.[8] There is evidence to suggest that the vessels in the injured area become passively dilated for a time after thawing. This dilatation is only relative, for although actual vasoconstriction may not be present, the caliber of the vessels can be altered by changes in the perfusion pressure. Therefore, the vasomotor tone of the arteries proximal to the injured area may be very important in determining the blood flow through the remainder of the extremity.[17] With the return of blood flow, edema begins to form as protein-rich fluid escapes through the capillary walls rendered hyperpermeable by the effects of cold or anoxia. Vesicles may also develop; the basal cell layer is commonly elevated from the dermis except for the rete pegs.[18] The edema progressively increases and may reach the maximal volume allowed by the extensile limit of the encompassing skin. After severe frostbite in rabbits the subcutaneous pressure at the time of the greatest foot volume is 25 cm. of water. As the edema fluid continues to be formed it is forced into the proximal normal tissues through interstitial spaces and lymphatic channels. After severe freezing of the rabbit's foot the fluid contains as much as 4.3 Gm. per cent of protein, or, on the average, 76 per cent of the plasma protein concentration before the frostbite. The circulating plasma protein concentration and plasma volume are reduced and the hematocrit rises under such circumstances at the peak of edema formation. These deviations from the normal become progressively smaller as hours pass by, due, according to Fuhrman and Crismon,[19] to diminishing protein loss and increased production of ultrafiltrate in the injured area.

Coincident with the formation of edema, stasis develops in the true capillaries.[15, 17, 20] The formed elements of the blood are seen progressively to fill the small vessels, bringing to a halt the circulation through them. This stasis is reversible, at least at the beginning. It has been shown that mechanical pressure or changes in blood flow in adjacent vessels will break up the red cell masses, the components of which then pass singly into the venous circulation.[21-23] There is some controversy as to the cause of the stasis. Three general possibilities have been considered. The view most widely held[20, 21, 22, 24] is that the capillary walls, rendered hyperpermeable by the injury, merely filter the cells out of the blood as the serum enters the interstitial spaces. According to this concept the phenomenon is described as silting. Kreyberg[21] has questioned the hypothesis that hyperpermeability alone is responsible for stasis on the grounds that it is not seen in the histamine reaction in which the capillaries are sufficiently hyperpermeable to produce edema fluid of protein content equal to that following frostbite. Furthermore, Tannenberg and Fisher[25] have reported that the red cells of blood drawn from an animal in which there is stasis behave differently from those of a normal animal. They concluded that stasis must be the result of some colloidal chemical alteration in blood unrelated to the clotting mechanism. This second possibility is supported by the observation of Friedman and Lange and their associates[26, 27] that the red cells begin to clump just before freezing occurs. They suggested that the cold agglutinins should be considered in this connection. The fact that, upon thawing, the red cells again become discrete before silting occurs, however, suggests that the cold agglutinins are not related to the

problem of stasis. The third possibility offered connects stasis with the sludging mechanism which Knisely and his colleagues[28] believed to be related to the early phase of the clotting phenomenon. They postulated precipitation on the cells of a "sticky coat" which causes them to adhere to one another and to the walls of the vessels. The failure of adequate heparinization to prevent stasis is held by some investigators[21, 22] to invalidate this theory. Lange, Weiner, and Boyd,[24] however, stated that heparinization prevents formation of "agglutinative thrombi" and, since the capillary hyperpermeability persists, it must be assumed that silting occurs but that the red blood cells do not stick together and later become discrete again.

After stasis has developed blood continues to flow through arteriovenous anastomoses and arteriolar venular capillaries. Accordingly, although the cross-sectional area of the vascular bed between arterioles and venules is reduced, Crismon and Fuhrman[17] expressed the belief that the minute volume of blood flow is increased as evidenced by the high skin temperature and the low arteriovenous oxygen difference. There results a large loss through arteriolar venular capillaries of plasma ultrafiltrate which cannot be reabsorbed through the true capillaries because of stasis, spatial distortion and kinking. This plasma filtrate, which is responsible for the dilution of the high protein concentration of the fluid just lost from the capillaries, is removed by passage into adjacent uninjured tissues and by the lymphatics. Since normal tissue meets increased metabolic demands by the opening of resting capillaries to increase the diffusion area, a process impossible in frostbite because of stasis, these authors believe gangrene is produced as a result of the discrepancy between the diffusion area and the increased metabolic needs caused by high tissue temperature. They also feel that cell survival is further endangered by the increased capillary-to-cell diffusion distance due to distension of tissues by edema fluid.

Although there is general concurrence in the course of events as described by Fuhrman and Crismon, there is not such agreement as to the significance of edema per se in causing death of tissue. Lange and Boyd[27] attributed tissue necrosis to vascular occlusion resulting from the conversion of the sludged blood to agglutinative thrombi and to later superimposed real thrombi. As evidence they offered the observation that agglutinative thrombi and subsequent gangrene may be prevented by heparinization. Kreyberg[15] felt both of these concepts to be wrong and he placed emphasis entirely upon stasis, which being by definition the absence of circulation, is sufficient to cause gangrene purely by oxygen lack. He believed the hyaline thrombi which are described as being organized from the silted red cells from three to eight days after injury merely represent necrosis of these cells *pari passu* with the surrounding tissue. This concept is at odds with that of Crismon and Fuhrman[29] who have stated that there may be recovery of frostbitten tissue without reopening of capillaries closed by stasis. They insisted that, if the degree of edema is controlled, tissues may be nourished adequately by plasma filtrate from arteriolar venular capillaries until new vessels have appeared. It has been our feeling, from our own experimental work and that of others, that tissue necrosis is not primarily related to edema per se but

rather to the anoxia and inadequate circulation dependent upon the stasis and vasoconstriction which follow frostbite and the thrombosis of vessels which results.

Following the development of edema, the frostbitten extremity tends to become moist from exudation of edema fluid and to become cyanotic. After the warm stage any tissue so severely injured that it will become necrotic cools progressively until its temperature approximates that of the environment; necrosis is then evident.[30] The gangrene usually appears wet at first, followed within a few days by mummification. An extremity which has survived without gangrene may show atrophy, degeneration and fibrosis.[16, 24, 26] Diffuse sclerosis may occur, apparently as the result of organization of the protein-rich edema fluid. There is also evidence[16] that structures high in lipid content, such as nerves, and muscles may be injured even when gross gangrene is avoided. It is interesting that the small nonmedullated vasoconstrictor fibers sometimes survive when other nerve fibers are injured. Obliterative endangiitis and sympathetic hyperactivity are not uncommon sequelae.

TREATMENT

The lack of agreement concerning what factor is most important in the production of gangrene following frostbite is reflected in the variety of therapeutic measures advocated for its prevention. Although animal experimentation has provided us with the best method for analyzing critically the worth of any method of treatment, certain precautions must be observed if the results of such study are to have validity. Unfortunately, there are certain rather unpredictable variations in the response of experimental animals to a given cold injury, necessitating especially careful control of the experimental procedure. We have found it essential to include in each experiment certain animals which will be set aside as untreated controls for comparison with the treated group. For some unexplained reason, the outcome of precisely the same cold injury repeated in any given laboratory from time to time will not necessarily be precisely the same. The factors of species and individual differences in cold resistance, acclimatization, seasonal variations, and dietary adequacy have been held responsible.[2, 21] It has also been found necessary to include in each experiment a certain number of animals which are treated by a method of known effectiveness. Otherwise, negative results cannot be properly evaluated. Unless experiments are so controlled the information derived from them may be confusing. It must also be recognized that various parts of experimental animals—ears, tails, and feet—vary considerably in vascularity and in the relative proportion of skin and muscle mass. Furthermore, there is some variation of vasomotor tonus from one species to another and from one part of the body to another. The safety with which animal experimentation in frostbite can be transferred to the problem in human beings is increased when similar results have been obtained in a number of different species and in frostbite of parts differing in their anatomical structure and in their vasomotor apparatus.

Slow Warming of the Frozen Part.—As the result of a suggestion made by Greene,[31] many cases of frostbite have been treated by exposing the injured

extremity to a cold atmosphere. Indeed, such treatment has over the years been the one most widely used. The basis for this method of treatment lay in the work of Lake and of Lewis. Lake[32] reported that tissue cultures survived exposure to cold longer at temperatures between -5° C. and +5° C. than at any temperature below 25° C. He attributed this occurrence to inhibition of metabolism at the lower temperatures while he thought that between 5° and 25° C. there was a reduction in the rate of anabolism but relatively little diminution of catabolism. Since Lewis and Love[13] thought that the major injury occurred at the time of thawing and was related to the edema which developed, they advised manual occlusion of the arteries during thawing. The artery was then to be gradually released so that there would be no sudden return of blood flow to the paralyzed vessels in the injured area. They feared that delivery of blood at or near arterial pressure to the capillaries rendered hyperpermeable by the injury would enhance the formation of edema and, hence, increase the loss of tissue. By maintaining the frozen extremity in an atmosphere of from 0° to 5° C., Greene believed that tissue could be kept at its optimal temperature for survival, the blood vessels maintained in a constricted state, and edema minimized. He suggested that the extremity be kept cold for from 6 to 21 days or until it could be warmed without causing pain or edema. Recently Rosenfeld and his associates[33] have made direct measurements of lymph flow, protein concentration and blood flow following frostbite of the feet of dogs. From the data they presented, no consistent time correlation between the peaks of blood flow and lymph flow or maximum edema formation after thawing can be discerned. As would be expected, however, the maximum lymph flow coincides with the attainment of the peak of accumulation of edema fluid. When one frostbitten foot of each of three dogs was immediately immersed in water at 10° C. there was no significant decrease in blood flow over that of the opposite control extremity. The increase in lymph flow and protein concentration as well as edema volume was slightly reduced and was delayed in the cold-treated legs as compared with the untreated frostbitten extremities, but eventually equal magnitude was attained in both.

Objections to this concept of treating frostbite with local cold have been raised on theoretical grounds.[18, 33, 34, 55] It has been pointed out that one cannot safely transpose the results obtained with isolated embryonic tissue in cultures to an intact animal where the situation is complicated by neurovascular interrelationships. Attention has been called to similar difficulties based upon purely physical considerations such as the difference between bathing a cell in frequently changed culture medium and transferring nutrient material from capillary to cell. Furthermore, there is no reason to believe that the vasoconstriction and the lack of dissociation of oxyhemoglobin produced by the cold would not more than offset any possible advantage derived from lowering the metabolism of the injured tissues.

Clinical reports of the use of this method of treatment are either uncontrolled or of insufficient number to be significant. Davis and his associates[18] described one case of bilateral high altitude frostbite of the hands in which one extremity was treated with cold packs for forty-eight hours while the other was exposed to air at ordinary room temperature. The cold-treated hand was more

TABLE I. RESULTS OF PROLONGED COOLING OF THE FROZEN EXTREMITY

AUTHOR	SPECIES	EXTREMITY FROZEN	NUMBER	TEMPERATURE OF FREEZING (IN ° C.)	DURATION FREEZING (IN MINUTES)	TREATMENT GIVEN	DETAILS OF TREATMENT	RESULTS*		
								EXCELLENT	GOOD OR EXCELLENT	POOR
Davis, Scarff, Rogers, and Dickinson, 1943	Man	Both hands	1	High altitude frostbite		Yes	One hand treated with cold packs 48 hr.	More pain, more severe cold sensitivity in treated hand		
Quintanilla, Knesen, and Essex, 1947	Rabbit	Foot	3	–42	3			Did not prevent edema		
				–45	1					
				–48	2					
Lange, Weiner, and Boyd, 1947	Man	Spot on forearm	4	–22	½	No		Gangrene		
			4	–22	½	Yes	Heparin begun 24 hr. later; cont'd 7 days	Almost no gangrene		
			4	–22	½	Yes	Ice bag 24 hr., then heparin for 7 days	Gangrene worse than with no treatment		
Fuhrman and Crismon, 1949	Rabbit	Foot	17	–55	3	No		0	0	17
			1	–54	3	Yes	Cooled in air at 15° C. for 4 hr.	0	0	1
			1	–54	3	Yes	Ice pack 7 hr.	0	0	1
Crismon and Fuhrman, 1949	Rabbit	Foot	9	–55	3	Yes	Plastic cast 5 to 7 days	0	3	6
			6	–55	3	Yes	Plastic cast 5 to 7 days chilled to 5 to 10° C. for 6 to 8 hr.	0	3	3
Lempke and Shumacker, 1949	Mouse	Tail	21	–15	5 sec.	No		1 (4.8)	6 (28.6)	15 (71.4)
			19	–15	5 sec.	Yes	Air cooled to 1-3° C. for 72 hours	0	0	19 (100)
			11	–15	5 sec.	Yes	Air cooled to 20° C. for 72 hr.	0	1 (9.1)	10 (90.9)
Lempke and Shumacker, 1951	Mouse	Foot	21	–15	½	No		3 (14.3)	18 (85.7)	3 (14.3)
			24	–15	½	Yes	Ice water 1 hr.	0	17 (70.8)	7 (29.2)

*In this and the following charts where such details are available excellent results are listed as those with no loss of tissue other than toenails, good results those in which loss of tissue is limited to toes, to the distal one cm. of tail, and less than the exposed area in case of frozen ears. Poor results are those with more extensive gangrene. Percentages are enclosed in parentheses.

uncomfortable, developed larger blisters, and was subsequently more sensitive to cold than the other.

Quintanilla and his colleagues[22] treated the frostbitten feet of three rabbits with ice packs for from one to six hours and stated only that edema was not prevented (Table I). Two feet of rabbits were treated with cold by Crismon and Fuhrman,[29] one for four hours with air cooled to 15° C. and one by application of an ice pack for seven hours, with no improvement over the results obtained in similarly injured untreated controls. These investigators also reported the study of three rabbits, the frozen feet of which were encased in a plastic cast and then cooled to from 5° to 10° C. for six to ten hours. They noted slight improvement over the result obtained by the use of casts alone. Lempke and Shumacker[14] placed the frozen feet of twenty-four mice in ice water for one hour and found that such treatment increased both the incidence and extent of the resultant gangrene as compared with that observed in twenty-one control animals. Lange, Weiner, and Boyd[24] reported that keeping a frozen spot on the forearms of human volunteers cooled with an icebag for twenty-four hours before administering heparin increased the amount of necrosis as compared with that observed when the arm was allowed to remain at room temperature for the same period before heparinization, or was not treated at all. All these studies do not comprise an entirely strict evaluation of Greene's method, to be sure, since the cooling period was brief or the temperature warmer than that he advocated. The most comprehensive experimental test of this thesis was reported in 1949 by Lempke and Shumacker.[36] Nineteen frozen tails of mice were treated by immediate exposure to air cooled to from 1° to 3° C. and this treatment was continued for three days. The resultant gangrene was definitely increased over that obtained in similarly exposed untreated tails.

The available experimental evidence provides a valid basis for the opinion that this method of treatment should be condemned as harmful, and indeed Greene[37] himself has ceased to support it. Some authors,[35, 38] however, continue to advocate a compromise measure, namely exposure of the injured extremity to a cool but not cold atmosphere. The experimental evidence available does not support this practice. In the experiments of Lempke and Shumacker[36] tails of mice so treated fared somewhat worse than untreated controls.

Plaster Casts and Pressure Dressings.—The belief of some investigators that gangrene following frostbite was in part due to spatial distortion, compression and kinking of capillaries by the edema fluid led to the trial of mechanical means of controlling edema. Crismon and Fuhrman[29] reported that application of closed plastic and plaster casts before and immediately after thawing, and of pressure dressings after the formation of maximal edema, reduced the amount of resultant gangrene in small numbers of rabbits with frostbite of the feet (Table II). If we consider only those feet frozen for three minutes at -55° C., we note that all seventeen of their untreated controls lost all the exposed tissue, while gangrene was limited to the toes in all encased in plaster. Similar limitation of tissue loss was obtained in three of nine feet treated with plastic casts

TABLE II. RESULTS OF TREATING FROZEN EXTREMITY WITH PLASTER CASTS AND PRESSURE DRESSINGS

AUTHOR	SPECIES	EXTREMITY FROZEN	NUMBER	TEMPERATURE OF FREEZING (IN ° C.)	DURATION FREEZING (IN MINUTES)	TREATMENT GIVEN	DETAILS OF TREATMENT	RESULTS		
								EXCELLENT	GOOD OR EXCELLENT	POOR
Lange and Boyd, 1945	Rabbit	Leg	11	−12 to −20	¾ to 1½	No		0	0	11
			2	−12 to −20	¾ to 1½	Yes		0	0	2
Crismon and Fuhrman, 1947	Rabbit	Foot	17	−55	3	No				17
			4	−55	3	Yes	Plaster cast 5 to 7 days	0	4	0
			9	−55	3	Yes	Plaster cast 5 to 7 days	0	3	6
			7	−55	3	Yes	Pressure dressing	0	4	3
			5	−55	2	No		0	4	1
			5	−55	2	Yes	Plaster cast 5 to 7 days	0	5	0
			5	−55	2	Yes	Pressure dressing	0	5	0
			4	−15	1	No		0	1	3
			4	−15	1	Yes	Plaster cast	0	2	2
			3	−15	1	Yes	Pressure dressing	0	3	0
Shumacker, Radigan, Ziperman, and Hughes, 1951	Mouse	Foot	20	−15	½	No		0	3 (15)	17 (85)
			15	−15	½	Yes	Plaster cast 10 days	0	2 (13)	13 (87)
	Rat	Foot	42	−20	⅓	No		0	17 (40.5)	25 (59.5)
			30	−20	⅓	Yes	Plaster cast 10 days	0	3 (6)	27 (94)
	Rabbit	Foot	21	−20	5	No		1 (4.8)	4 (19.1)	17 (80.9)
			10	−20	5	Yes	Plaster cast 10 days	0	1 (10)	9 (90)

and in four of seven treated with pressure dressings. Although the results were not quite as good as those obtained from the most effective method of treatment, namely rapid warming, these authors stated that the functional result was better because there was less late scarring, due presumably to organization of the protein-rich interstitial edema fluid.

Lange and Boyd[27] used pressure dressings on the legs of two rabbits with, and without, heparinization. Results were the same as those ordinarily obtained in animals similarly treated without the pressure dressings. However, no information was given as to the length of time the dressings were maintained. Fuhrman and Crismon felt that this method of treatment was without benefit unless it was continued for at least from five to seven days. Quintanilla and his associates[22] stated that pressure dressings and plaster casts were ineffective, but they did not give the data upon which this observation was based.

In experiments dealing with larger numbers of mice, rats, and rabbits conducted with more precise control of the initial injury as well as of the possible harmful effects of the casts themselves, Shumacker and his colleagues[39] demonstrated that plaster casts left in place for ten days were without benefit and, in the case of the rat's foot, were actually harmful. Similar casts applied to normal feet were tolerated without any adverse effect. These results have strengthened our conviction that the role of edema per se is not as important in the pathogenesis of gangrene as Fuhrman and Crismon believed. Indeed, in a study of the magnitude of edema following frostbite of the mouse's foot treated by a variety of measures, no consistent correlation was noted between the amount of the edema and the anticipated end result except that those feet which might be expected to recover lost their edema earlier than was the case when methods had been employed which experience had demonstrated to be of little or no benefit. This study, however, was subject to the possible criticism that only the edema in the feet—the part frozen—was measured and that swelling of the feet might reasonably be expected to be the same in all, regardless of treatment, because of the limitations to expansion imposed by the encompassing skin. Following a severe injury such as was inflicted in this case the edema fluid always extends into the tissue proximal to that frostbitten. To overcome this objection an experiment was performed in which the feet of rabbits were frozen and the change in volume of the feet and legs together measured. This method does not measure the total amount or rate of edema formed but rather the excess of edema fluid produced over that absorbed. However, it is the factor of distention of tissue with fluid which primarily concerns those who believe edema to be important in the pathogenesis of gangrene in frostbite.

One hind leg of each of sixteen rabbits previously anesthetized with pentobarbital sodium was closely clipped. The volume of each was measured by its displacement of water from a graduated glass cylinder. This method of measuring the volume of a leg in our hands gives reproducible results within ±3 per cent. The feet were then frozen by immersion up to the hock in an ether bath cooled to -20° C. and maintained at that temperature for five minutes after solidification. Eight of the feet were then immediately thawed by immersion

in water at 42° C. for two minutes. The remainder were allowed to thaw spontaneously at room temperature (26° C.). Feet so treated require thirty minutes to thaw completely. Repeat measurements of the leg volume were made at one, four, and twenty-three hours after freezing and on the second, fourth, and fifth days after injury. An additional determination at one and a half hours was made in the case of the feet thawed slowly. The data obtained are presented in Fig. 1 as the percentage change in leg volume from the original volume which is considered 100 per cent. There was no significant difference in the rate or degree of edema accumulation between the two groups until the second day. On the second and fourth days after frostbite the edema in the rapidly thawed extremities had decreased to a significant extent as compared to the

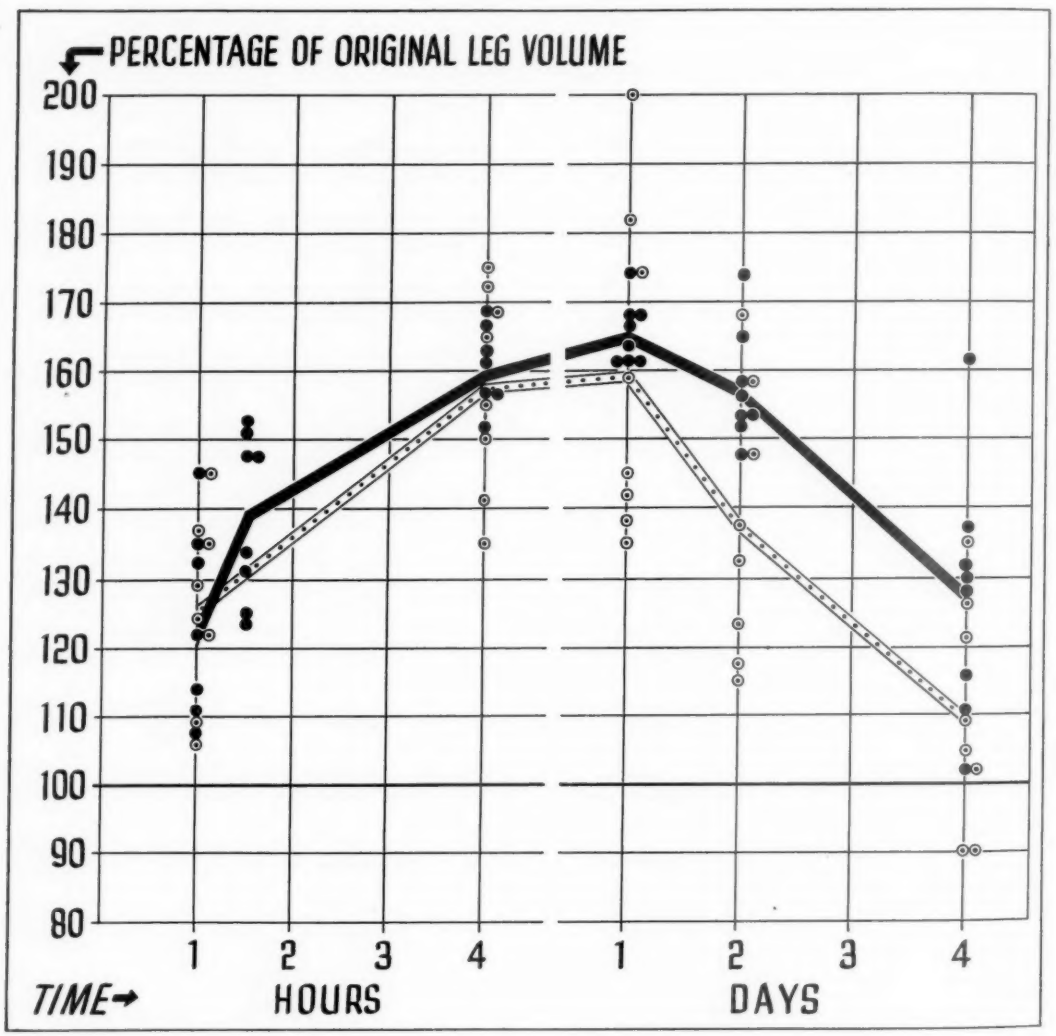

Fig. 1.—Chart indicating the effect of immediate rapid thawing of the frozen rabbit's foot upon edema of the leg. Values are expressed in percentage of original leg volume. Solid circles and solid line represent measurements and mean values in treated controls; open circles and dotted line represent values in animals treated by rapid thawing. Statistical analysis of data reveals no significant difference except for observations made on second and fourth days.

control group. One (14.3 per cent) of the control group survived without gangrene as compared to three (37.5 per cent) of the treated group. The end results as regards limiting tissue loss to the toes were one (14.3 per cent) and seven (87.5 per cent) respectively. These results confirm our original observation that there is no consistent difference between the amount of edema formed after frostbite and the end result except that those extremities which are to recover absorb the edema more rapidly than those which are to become gangrenous.

Immediate Rapid Warming of the Frozen Part.—The most convincing argument against the use of locally applied cold or slow thawing in the treatment of frostbite has been the remarkable efficacy of the immediate application of moderate warmth to the froden extremity in order to thaw it rapidly. Contrary to expectations based on philosophic reasoning and uncontrolled clinical observations,[1, 2, 3, 13, 32] rapid thawing has proved to be the most effective single method for preventing gangrene in frostbite. Microscopic study of the vascular reaction following rapid thawing revealed that stasis was delayed for several hours until the time of maximum formation of edema.[17]

Harkins and Harmon[40] in 1937 compared rapid and slow thawing of frozen legs of dogs and ears of rabbits; they felt that no conclusion could be reached other than that rapid thawing did not increase tissue damage. In 1939 Ariev[41] demonstrated that thawing the frozen ears and feet of rabbits rapidly by immersing them in water kept at 42° C. reduced the expected incidence of gangrene (Table III). Once thawed, the previously frozen extremities were exposed to ordinary room temperatures. Using a more standard injury of the ears and feet of rabbits, Fuhrman and Crismon[42] were able to confirm the increased salvage of injured tissue obtained with this treatment. Subsequently, Shumacker and his colleagues[14, 36, 29, 43] have in a number of experiments using ears, tails and feet of several species of animals firmly established the superiority of this method of treatment. Only Quintanilla and his associates[22] have not reported favorably and they gave no details of the conditions of their study so that analysis of it is impossible. Except for their work, rapidly thawing the frozen part has always reduced the incidence and extent of gangrene over that observed in similarly injured but untreated control animals, although its absolute efficacy decreases with the severity of the injury.[14]

The conditions under which rapid thawing is performed are important. The most favorable results in experimental animals are obtained when this is accomplished by immersion of the frozen part in water kept at 42° C. and when such exposure is continued only until the extremity has become thawed and warm. It has been shown[43] that rapid thawing at 38° C. is not as effective as thawing at 42° C. and that the use of temperatures as high as 50° C. may actually be harmful. Furthermore, when the frozen tails of mice were first thawed rapidly and then were kept in an atmosphere of 40° for seventy-two hours, the resultant gangrene was greater than in the case of those allowed to remain at room temperature following immediate warming.[36]

Fuhrman and Crismon[42] noted a high incidence of rather incapacitating scarring of tissue of limbs saved from gangrene by rapid thawing and advocated[29]

TABLE III. RESULTS OF TREATING FROSTBITE BY IMMEDIATE RAPID WARMING OF FROZEN PART

AUTHOR	SPECIES	EXTREMITY FROZEN	NUMBER	TEMPERATURE OF FREEZING (IN ° C.)	DURATION FREEZING (IN MINUTES)	TREATMENT GIVEN	DETAILS OF TREATMENT	RESULTS		
								EXCELLENT	GOOD OR EXCELLENT	POOR
Ariev, 1939	Rabbit	Ear	5	Ethyl chloride spray		No				5
			5	Ethyl chloride spray		Yes	Compresses at 40 to 45° C.	5		
		Foot		Ethyl chloride spray		No				All
				Ethyl chloride spray		Yes	Compresses at 35 to 40° C.			
Fuhrman and Crismon, 1947	Rabbit	Ear	11	−55	1	No				11
			6	−55	1	Yes	Water 42° C. for ¼ to 2 min.	4	5	1
			24	−55	1½	No				24
			3	−55	1½	Yes	Water 42° C. for ¼ to 2 min.	1	2	1
			2	−55	2	No				2
			1	−55	2	Yes	Water 42° C. for ¼ to 2 min.			1
		Foot	16	−55	3	No			1	15
			7	−55	3	Yes	Water 42° C. for 2 to 5 min.	0	6	1
			4	−15	1	No				4
			5	−15	1	Yes	Water 42° C. for 2 to 5 min.	1	5	0
Lempke and Shumacker, 1949	Mouse	Tail	21	−15	5 sec.	No		1 (4.8)	6 (28.6)	15 (71.4)
			19	−15	5 sec.	Yes	Water 42° C. for 2 min.	14 (73.7)	16 (82.2)	3 (15.8)
			14	−15	5 sec.	Yes	Water 42° C. for 2 min.; air 40° C. for 72 hr.	4 (28.6)	9 (64.3)	5 (35.7)
Finneran and Shumacker, 1950	Mouse	Tail	44	−15	5 sec.	No		2 (4.5)	4 (9.1)	40 (90.9)
			40	−15	5 sec.	Yes	Water 42° C. for 2 min.	7 (17.5)	26 (65)	14 (35)
		Foot	36	−20	5 sec.	No		0	2 (5.6)	34 (94.4)
			25	−20	5 sec.	Yes	Water 42° C. for 2 min.	12 (48)	19 (76)	6 (24)
	Rat	Tail	43	−15	5 sec.	No		4 (8.8)	6 (13.7)	37 (86.3)
			47	−15	5 sec.	Yes	Water 42° C. for 2 min.	24 (51)	34 (72.3)	13 (27.7)
		Foot	22	−20	5 sec.	No		0	11 (50)	11 (50)
			31	−20	5 sec.	Yes	Water 42° C. for 2 min.	12 (38.8)	27 (87.6)	4 (12.4)

	Rabbit	Ear	39	−15	2	No			
			20	−15	2	Yes	Water 42° C. for 2 min.	15 (75)	19 (85)	1 (5)
		Foot	12	−15	5	No		0	0	12 (100)
			15	−15	5	Yes	Water 42° C. for 2 min.	7 (46.7)	15 (100)	0
	Dog	Foot	20	−25	15	No		3 (15)	4 (20)	16 (80)
			9	−25	15	Yes	Water 42° C. for 2 min.	1 (11.1)	6 (66.7)	3 (33.3)
Shumacker, Radigan, Ziperman, and Hughes, 1951	Mouse	Tail	64	−15	5 sec.	No		4 (6.3)	9 (14.1)	55 (85.9)
			60	−15	5 sec.	Yes	Water 42° C. for 2 min.	14 (23.3)	37 (61.6)	23 (38.4)
		Foot	20	−15	½	No		0	3 (15)	17 (85)
			25	−15	½	Yes	Water 42° C. for 2 min.	11 (44)	20 (80)	5 (20)
	Rat	Tail	15	−20	15 sec.	No		0	0	15
			15	−20	15 sec.	Yes	Water 42° C. for 2 min.	1 (6.7)	2 (13.3)	13 (86.7)
		Foot	42	−20	⅓	No		0	17 (40.5)	25 (59.5)
			20	−20	⅓	Yes	Water 42° C. for 2 min.	15 (75)	20 (100)	0
	Rabbit	Ear	22	−20	2	No		0	1 (4.5)	21 (95.5)
			18	−20		Yes	Water 42° C. for 2 min.	6 (33.3)	16 (88.9)	2 (11.1)
		Foot	21	−20	5	No		1 (4.8)	4 (19.1)	17 (80.9)
			14	−20	5	Yes	Water 42° C. for 2 min.	9 (64.3)	14 (100)	0
Lempke and Shumacker, 1951	Mouse	Foot	36	−15	½	No		16 (44.4)	34 (94.4)	2 (5.6)
			49	−15	½	Yes	Water 42° C. for 2 min.	46 (93.9)	49 (100)	0
			45	−15	2⅙	No		1 (2.2)	8 (17.8)	37 (82.2)
			51	−15	2⅙	Yes	Water 42° C. for 2 min.	14 (27.5)	43 (84.4)	8 (15.6)
	Rat	Foot	14	−20	⅓	No		11 (78.6)	14 (100)	0
			11	−20	⅓	Yes	Water 42° C. for 2 min.	10 (90.9)	11 (100)	0
	Rabbit	Foot	15	−20	5	No		0	0	15
			7	−20	5	Yes	Water 42° C. for 2 min.	1 (14.3)	6 (85.7)	1 (14.3)

the use of casts or pressure dressings following thawing in order to force the edema from the injured extremity. Such pressure dressings and casts resulted in less scarring but increased somewhat the incidence and extent of loss of tissue. They as well as others have reported an increased amount of edema with this method of treatment. As mentioned previously, however, we have not been able to confirm this impression but on the contrary have shown that rapid thawing does not always result in greater edema but does tend to bring about more rapid subsidence of the edema than in untreated controls. Rosenfeld and his associates,[33] by direct measurements of blood and lymph circulation in the extremities of dogs following frostbite, also found no increase in edema formation after rapid thawing over that observed in similarly injured untreated feet. In our experience it is also interesting that insignificant scarring has been noted in frozen parts treated effectively by rapid thawing; except for the ears of rabbits, extremities satisfactorily treated by rapid thawing are difficult or impossible to differentiate from normal extremities.

The principal objection to the use of rapid thawing as a practical method for treating clinical frostbite has been that it would be impractical under the conditions in which frostbite occurs. It should, however, be possible to solve this problem.

Anticoagulants.—The possibility that anticoagulants might be of value in the treatment of frostbite was first investigated in 1944 by Brambel and Loker,[44] who used Dicumarol in the treatment of a single patient. The following year Lange, Boyd, and Loewe[45] reported experimental observations which were convincing of the dramatic efficacy of heparinization in the prevention of gangrene. In several experiments Lange and his associates[24, 27, 45, 46] have been able to prevent gangrene in approximately 85 per cent of cases by heparinization, whereas all of the untreated controls sustained extensive loss of tissue (Table IV). Treatment was begun within four hours of injury in all cases except for spot-freezing of the arms of seven human volunteers, when it was delayed twenty-four hours. The results were only slightly less striking than with immediate treatment. The possible usefulness of heparin therapy was based upon the observation that tissue necrosis does not begin until the silted red blood cells become converted to hyalin thrombi, approximately seventy-two hours after frostbite in the rabbit. Lange and his associates feel that heparinization begun anytime before seventy-two hours have elapsed following frostbite should have some beneficial effect in proportion to the number of vessels still remaining unoccluded by thrombus. In all circumstances it is emphasized that heparinization must be maintained continuously for a period of five to seven days with prolongation of coagulation time to around twenty-two to thirty minutes. When single or repeated episodes occurred during which the coagulation time dropped below this level, only about 25 per cent of the animals survived without gangrene.

Numerous investigators have attempted to reproduce the results reported by Lange and his colleagues with indifferent success. It is possibly significant that none of these workers has followed and controlled the level of heparinization as closely as Lange's group has done. However, Shumacker and his associates,[47]

control group. One (14.3 per cent) of the control group survived without gangrene as compared to three (37.5 per cent) of the treated group. The end results as regards limiting tissue loss to the toes were one (14.3 per cent) and seven (87.5 per cent) respectively. These results confirm our original observation that there is no consistent difference between the amount of edema formed after frostbite and the end result except that those extremities which are to recover absorb the edema more rapidly than those which are to become gangrenous.

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								EXCELLENT	GOOD OR EXCELLENT	POOR
Ariev, 1939	Rabbit	Ear	5	Ethyl chloride spray		No				5
			5	Ethyl chloride spray		Yes	Compresses at 40 to 45° C.	5		
		Foot		Ethyl chloride spray		No				All
				Ethyl chloride spray		Yes	Compresses at 35 to 40° C.			
Fuhrman and Crismon, 1947	Rabbit	Ear	11	−55	1	No				11
			6	−55	1	Yes	Water 42° C. for ¼ to 2 min.	4	5	1
			24	−55	1½	No				24
			3	−55	1½	Yes	Water 42° C. for ¼ to 2 min.	1	2	1
			2	−55	2	No				2
			1	−55	2	Yes	Water 42° C. for ¼ to 2 min.			1
		Foot	16	−55	3	No			1	15
			7	−55	3	Yes	Water 42° C. for 2 to 5 min.	0	6	1
			4	−15	1	No				4
			5	−15	1	Yes	Water 42° C. for 2 to 5 min.	1	5	0
Lempke and Shumacker, 1949	Mouse	Tail	21	−15	5 sec.	No		1 (4.8)	6 (28.6)	15 (71.4)
			19	−15	5 sec.	Yes	Water 42° C. for 2 min.	14 (73.7)	16 (82.2)	3 (15.8)
			14	−15	5 sec.	Yes	Water 42° C. for 2 min.; air 40° C. for 72 hr.	4 (28.6)	9 (64.3)	5 (35.7)
Finneran and Shumacker, 1950	Mouse	Tail	44	−15	5 sec.	No		2 (4.5)	4 (9.1)	40 (90.9)
			40	−15	5 sec.	Yes	Water 42° C. for 2 min.	7 (17.5)	26 (65)	14 (35)
		Foot	36	−20	5 sec.	No		0	2 (5.6)	34 (94.4)
			25	−20	5 sec.	Yes	Water 42° C. for 2 min.	12 (48)	19 (76)	6 (24)
	Rat	Tail	43	−15	5 sec.	No		4 (8.8)	6 (13.7)	37 (86.3)
			47	−15	5 sec.	Yes	Water 42° C. for 2 min.	24 (51)	34 (72.3)	13 (27.7)
		Foot	22	−20	5 sec.	No		0	11 (50)	11 (50)
			31	−20	5 sec.	Yes	Water 42° C. for 2 min.	12 (38.8)	27 (87.6)	4 (12.4)

	Rabbit	Ear	39	−15	2	No	0	2 (5.1)	37 (94.9)
			20	−15	2	Yes Water 42° C. for 2 min.	15 (75)	19 (85)	1 (5)
		Foot	12	−15	5	No	0	0	12 (100)
			15	−15	5	Yes Water 42° C. for 2 min.	7 (46.7)	15 (100)	0
	Dog	Foot	20	−25	15	No	3 (15)	4 (20)	16 (80)
			9	−25	15	Yes Water 42° C. for 2 min.	1 (11.1)	6 (66.7)	3 (33.3)
Shumacker, Radigan, Ziperman, and Hughes, 1951	Mouse	Tail	64	−15	5 sec.	No	4 (6.3)	9 (14.1)	55 (85.9)
			60	−15	5 sec.	Yes Water 42° C. for 2 min.	14 (23.3)	37 (61.6)	23 (38.4)
		Foot	20	−15	½	No	0	3 (15)	17 (85)
			25	−15	½	Yes Water 42° C. for 2 min.	11 (44)	20 (80)	5 (20)
	Rat	Tail	15	−20	15 sec.	No	0	0	15
			15	−20	15 sec.	Yes Water 42° C. for 2 min.	1 (6.7)	2 (13.3)	13 (86.7)
		Foot	42	−20	⅓	No	0	17 (40.5)	25 (59.5)
			20	−20	⅓	Yes Water 42° C. for 2 min.	15 (75)	20 (100)	0
	Rabbit	Ear	22	−20	2	No	0	1 (4.5)	21 (95.5)
			18	−20		Yes Water 42° C. for 2 min.	6 (33.3)	16 (88.9)	2 (11.1)
		Foot	21	−20	5	No	1 (4.8)	4 (19.1)	17 (80.9)
			14	−20	5	Yes Water 42° C. for 2 min.	9 (64.3)	14 (100)	0
Lempke and Shumacker, 1951	Mouse	Foot	36	−15	½	No	16 (44.4)	34 (94.4)	2 (5.6)
			49	−15	½	Yes Water 42° C. for 2 min.	46 (93.9)	49 (100)	0
			45	−15	2⅙	No	1 (2.2)	8 (17.8)	37 (82.2)
			51	−15	2⅙	Yes Water 42° C. for 2 min.	14 (27.5)	43 (84.4)	8 (15.6)
	Rat	Foot	14	−20	⅓	No	11 (78.6)	14 (100)	0
			11	−20	⅓	Yes Water 42° C. for 2 min.	10 (90.9)	11 (100)	0
	Rabbit	Foot	15	−20	5	No	0	0	15
			7	−20	5	Yes Water 42° C. for 2 min.	1 (14.3)	6 (85.7)	1 (14.3)

the use of casts or pressure dressings following thawing in order to force the edema from the injured extremity. Such pressure dressings and casts resulted in less scarring but increased somewhat the incidence and extent of loss of tissue. They as well as others have reported an increased amount of edema with this method of treatment. As mentioned previously, however, we have not been able to confirm this impression but on the contrary have shown that rapid thawing does not always result in greater edema but does tend to bring about more rapid subsidence of the edema than in untreated controls. Rosenfeld and his associates,[33] by direct measurements of blood and lymph circulation in the extremities of dogs following frostbite, also found no increase in edema formation after rapid thawing over that observed in similarly injured untreated feet. In our experience it is also interesting that insignificant scarring has been noted in frozen parts treated effectively by rapid thawing; except for the ears of rabbits, extremities satisfactorily treated by rapid thawing are difficult or impossible to differentiate from normal extremities.

The principal objection to the use of rapid thawing as a practical method for treating clinical frostbite has been that it would be impractical under the conditions in which frostbite occurs. It should, however, be possible to solve this problem.

Anticoagulants.—The possibility that anticoagulants might be of value in the treatment of frostbite was first investigated in 1944 by Brambel and Loker,[44] who used Dicumarol in the treatment of a single patient. The following year Lange, Boyd, and Loewe[45] reported experimental observations which were convincing of the dramatic efficacy of heparinization in the prevention of gangrene. In several experiments Lange and his associates[24, 27, 45, 46] have been able to prevent gangrene in approximately 85 per cent of cases by heparinization, whereas all of the untreated controls sustained extensive loss of tissue (Table IV). Treatment was begun within four hours of injury in all cases except for spot-freezing of the arms of seven human volunteers, when it was delayed twenty-four hours. The results were only slightly less striking than with immediate treatment. The possible usefulness of heparin therapy was based upon the observation that tissue necrosis does not begin until the silted red blood cells become converted to hyalin thrombi, approximately seventy-two hours after frostbite in the rabbit. Lange and his associates feel that heparinization begun anytime before seventy-two hours have elapsed following frostbite should have some beneficial effect in proportion to the number of vessels still remaining unoccluded by thrombus. In all circumstances it is emphasized that heparinization must be maintained continuously for a period of five to seven days with prolongation of coagulation time to around twenty-two to thirty minutes. When single or repeated episodes occurred during which the coagulation time dropped below this level, only about 25 per cent of the animals survived without gangrene.

Numerous investigators have attempted to reproduce the results reported by Lange and his colleagues with indifferent success. It is possibly significant that none of these workers has followed and controlled the level of heparinization as closely as Lange's group has done. However, Shumacker and his associates,[47]

using a less severe and less extensive cold injury and presumably more adequate heparinization, observed beneficial effects only in 35 per cent of their rabbits. In a small series of rabbits in which the onset of treatment was delayed for two to ten hours the results were of the same order. In all of thirty animals, however, only three survived without any loss of tissue.

Treating frostbite of the tails of mice, Lempke and Shumacker[36] were able to prevent gangrene in 39 per cent of animals when heparin was administered every three hours and to limit damage to minimal loss of tissue in another 39 per cent. When the treatment schedule was changed to injections of heparin every four hours, the results were no better than in the control group which escaped gangrene in 4.8 per cent and sustained minor necrosis in another 23.8 per cent. A subsequent study of frostbite in the rat by Finneran and Shumacker[43] yielded results which were suggestive but were not consistently significant. Furthermore, when heparinization was delayed for three hours after the cold injury, the results were generally poorer than when treatment was begun immediately. Quintanilla and his group[22] were unable to detect any improvement with heparin treatment carried out for thirty-six hours. It is possible that the duration of treatment was too short although they do state that gangrene was becoming evident at this time. Pichotka and Lewis[48] reported that they were unable to demonstrate any prevention of gangrene by anticoagulant therapy. However, as Lange, Boyd, and Weiner[46] have pointed out, their treatment was not controlled completely by clotting time determinations and the small series of five animals which received the most vigorous treatment, that is, 20 mg. each four hours for six days, did show a decreased incidence of extensive necrosis. It is also true that these authors did state[46] that in an unpublished study of combined heparin and Dicumarol therapy, they were able to save 60 per cent of the tissue that was lost in the control animals. In a very small series of rabbits with frozen feet, Fuhrman and Crismon[49] were unsuccessful in preventing gangrene with heparin and with Dicumarol.

Lange and his associates[24] have reported the successful treatment with heparin of two cases of frostbite of the hands of men, sufficiently severe that they would have judged that gangrene would ordinarily have followed.

Sympathetic Blockade.—Sympathetic nerve interruption, like other methods of increasing the blood supply to a frozen extremity, was for a long time condemned without trial as being harmful.[1, 2, 50] Because the appearance of edema coincided with the stage of reactive hyperemia, it was thought that the increased blood flow was responsible for gangrene by enhancing the formation of edema. Furthermore, it was thought that the sympathetic nerves had been rendered functionless by the cold injury; therefore, it was argued that sympathetic interruption could have no effect but that if it should have an effect, it would be harmful. Kreyberg,[51] in studying the effect of previous sympathectomy upon the results of spot-freezing of the rabbit's ear, reported that edema formation was more fulminating and extensive in such extremities than in normally innervated controls. However, he found the resultant damage to be less severe. In a later publication[21] he contradicted this last observation, stating that the

TABLE IV. RESULTS OF ANTICOAGULANT THERAPY IN TREATMENT OF FROSTBITE

AUTHOR	SPECIES	PART FROZEN	NUMBER	TEMPERATURE OF FREEZING (IN ° C.)	DURATION FREEZING (IN MINUTES)	TREATMENT GIVEN	DETAILS OF TREATMENT	RESULTS		
								EXCELLENT	GOOD OR EXCELLENT	POOR
Lange, Boyd, and Loewe, 1945	Rabbit	Spot on abdomen	5	Beaker of CO_2 (about −22)	5 to 90	No				All frozen over 15 min.
			5	Beaker of CO_2 (about −22)	5 to 90	Yes	Heparin started within ½ to 3 hr.; 30 mg. q. 12 hr. for 5 days	3	5	
		Leg	11	−12 to −20	45 to 90	No		0	0	20
			11	−12 to −20	45 to 90	Yes	Heparin	9	11	0
Lange, Weiner, and Boyd, 1947	Rabbit	Leg	20	−30	30	No		0	0	20
			21	−30	30	Yes	Heparin 30 mg. q. 12 hr.	18	21	0
	Man	Spot on arm 5 diameter cm.	3	About −30	30	No		Gangrene		
			3	About −30	30	Yes	Heparin by IV drip for 7 days	No gangrene		
			3	About −30	30	Yes	Heparin by IV, begun 24 hr. after injury	Almost no gangrene		
			3	About −30	30	Yes	Heparin by IV + local use of electric pad	Gangrene almost as severe as in untreated controls		
			3	About −30	30	Yes	Electric pad, no heparin	Gangrene worse than in controls		
		Spot on arm 2 cm. diameter	1	About −22	10	No		Necrosis, 1 by 0.3 to 0.5 cm.		
			3	About −22	10	Yes	Heparin in Pitkin's for 6 days	No deep injury		
			4	About −22	30	No		Necrosis, 1 by 0.3 to 0.5 cm.		
			4	About −22	30	Yes	Heparin in Pitkin's for 6 days	No deep injury		
		Spot on arm 3.5 cm. diameter	4	About −22	30	No		Gangrene		
			4	About −22	30	Yes	Heparin by IV drip for 6 days	No gangrene		
			4	About −22	30	Yes	Heparin by IV drip for 6 days, started 24 hr. after injury	Almost no gangrene		
			4	About −22	30	Yes	Ice bag 24 hr., then heparin by IV drip for 6 days	Gangrene worse than in untreated controls		
Quintanilla, Knesen, and Essex, 1947	Rabbit	Foot	3	−20	20	No		0	0	3
			3	−20	20	Yes	Heparin, 1000 u. be-	0	0	3

Quintanilla, Knesen, and Essex, 1947	Rabbit	Foot	3	−20	20	No		0	0	3
			3	−20	20	Yes	Heparin, 1000 u. before injury then 500 u. q. 3 hr. for 36 hr.	0	0	3
Shumacker, White, Wrenn, Cordell, and Sanford, 1947	Rabbit	Foot	3	−12 to −20	60	No		0	0	3
			8	−12 to −20	60	Yes	Heparin 20 to 30 mg. q. 4 hr. for 48 to 144 hr., started 30 min. after injury	0	3	5
			7	−12 to −20	30	No		0	0	7
			8	−12 to −20	30	Yes	Heparin 20 to 30 mg. q. 4 hr. for 64 to 144 hr. starting 30 min. after injury	1	0	7
			4	−12 to −20	30	Yes	Heparin 20 mg. q. 4 hr. for 144 hr., starting 2 to 10 hr. after injury	0	2	2
			4	−12 to −20	10	No		0	0	4
			9	−12 to −20	10	Yes	Heparin 20 mg. q. 4 hr. for 48 to 144 hr., starting 30 min. after injury	2	5	4
			1	−12 to −20	10	Yes	Heparin 20 mg. q. 4 hr. for 144 hr., starting 10 hr. after injury	0	0	1
Lempke and Shumacker, 1949	Mouse	Tail	21	−15	5 sec.	No		1 (4.8)	6 (28.6)	15 (71.4)
			18	−15	5 sec.	Yes	Heparin 0.15 mg. q. 4 hr. × 4, then q. 3 hr. × 2, then 0.1 mg. q. 3 hr. × 20	7 (38.9)	14 (77.8)	4 (22.2)
			9	−15	5 sec.	Yes	Heparin 0.2 mg. q. 3 hr. × 4, then q. 4 hr. × 15	0	3 (33.3)	6 (66.7)
Pichotka and Lewis, 1949	Rabbit	Leg	35	−25	30	No		0	7 (20)	28 (80)
			5	−25	30	Yes	Heparin 20 mg. q. 4 hr. for 6 days, started within 12 hr. of injury	0	3	2
			27	−25	30	Yes	Heparin 30 mg. q. 6 hr.	0	4 (14.8)	23 (85.2)
			13	−25	30	Yes	Heparin 30 mg. q. 12 hr.	0	1 (7.7)	12 (92.3)
			32	−15	30	No		4 (12.5)	20 (62.5)	12 (37.5)
			46	−15	30	Yes	Heparin 30 mg. q. 6 hr. for 6 days	3 (6.5)	24 (52.2)	22 (47.8)

TABLE IV.—CONT'D

AUTHOR	SPECIES	PART FROZEN	NUMBER	TEMPERATURE OF FREEZING (IN ° C.)	DURATION FREEZING (IN MINUTES)	TREATMENT GIVEN	DETAILS OF TREATMENT	RESULTS		
								EXCELLENT	GOOD OR EXCELLENT	POOR
Finneran and Shumacker, 1950	Rat	Tail	43	−15	5 sec.	No		4 (8.8)	6 (13.7)	37 (86.3)
			39	−15	5 sec.	Yes	Heparin 1 mg. q. 3 hr. × 4, then 0.5 mg. q. 3 hr. × 21	7 (17.9)	11 (28.1)	28 (71.9)
			46	−15	5 sec.	Yes	Heparin 1 mg. q. 3 hr. × 4, then 0.5 mg. q. 3 hr. × 21 starting 3 hr. after injury	6 (13)	9 (19.5)	37 (80.5)
		Foot	22	−20	5 sec.	No		0	11 (50)	11 (50)
			38	−20	5 sec.	Yes	Heparin 1 mg. q. 3 hr. × 4, then 0.5 mg. q. 3 hr. × 21	7 (18.4)	22 (57.9)	16 (42.1)
			41	−20	5 sec.	Yes	Heparin 1 mg. q. 3 hr. × 4, then 0.5 mg. q. 3 hr. × 21 starting 3 hr. after injury	2 (4.9)	28 (68.3)	13 (31.7)
Fuhrman and Crismon, 1950	Rabbit	Foot	16	−55	3	No			1	15
			2	−55	3	Yes	Dicumarol 5 to 10 mg./kg. before frostbite			2
			2	−55	3	Yes	Heparin 10 mg./kg. q. 24 hr. for 3 days in one, q. 12 hr. for 3 days in other			2
			5	−55	2	No			4	1
			1	−55	2	Yes	Heparin 10 mg./kg. q. 8 hr. for 3 days			1
Lange, Boyd, and Weiner, 1950	Rabbit	Leg	32	−12 to −30	30 to 45	No		0	0	32
			34	−12 to −30	30 to 45	Yes	Heparin for 5+ days (coag. time > 30 min.)	29 (85.5)		5 (14.5)
			17	−12 to −30	30 to 45	Yes	Heparin for 5+ days (coag. time > 30 min.)	4 (23.5)		13 (76.5)

damage was equal to that of the normal area. Rödén[52] in a study of twelve rabbits treated by unilateral chemically (phenol) produced periarterial sympathectomy 12 to 165 minutes after frostbite of both feet concluded that early sympathetic denervation caused more edema and tissue loss than no treatment at all and that denervation after two hours was without effect. However, the data represented to substantiate the effectiveness of his sympathetic interruption are not convincing. The skin temperature elevations were slight, short-lived and variable as to the time of appearance. Moreover, femoral periarterial sympathectomy is not an effective method of denervating the foot. Lempke and Shumacker[53] recorded the foot volume and skin temperature of dogs which had had a unilateral lumbar sympathectomy before frostbite of both hind extremities and found no significant difference between the two in either respect.

Following the discovery that rapid warming delayed the appearance of stasis, Crismon and Fuhrman[17] studied the effect of sympathetic procaine block in order to determine whether that phenomenon was due to an alteration in blood flow or to some other action. They had previously made observations[30] which confirmed Tittel's report that the vessels in the injured area were paralyzed immediately following frostbite and that their dilatation was only relative and depended upon perfusion pressure. Sympathetic anesthesia did delay the development of stasis, presumably by relaxing the constriction of the vessels proximal to the injured area and thereby increasing the intravascular pressure within the frostbitten vessels. Extensive vasoconstriction in the frostbitten extremity has been noted by several workers.[5, 7, 8, 17, 20, 27] There is also evidence to suggest that blood flow is not at its maximum during the phase of so-called reactive hyperemia[8] and that the sympathetic vasoconstrictor nerve fibers often survive in the presence of inactivation by cold of the other fibers in the same nerve bundle.[16] These observations would suggest that sympathetic interruption might be beneficial in the early treatment of frostbite. The situation is somewhat similar to that seen following combined traumatic neurovascular injury to an extremity. Although the limb is hyperemic, the circulation may still be increased by sympathetic interruption.[54]

Fuhrman and Crismon[49] did not obtain any decrease in the amount of gangrene which developed in the frozen ears of rabbits treated with stellate blocks performed either once immediately after freezing or repeated once the following day (Table V). Lempke and Shumacker[56] treated the frozen tails of mice by the administration of tetraethylammonium chloride for seventy-two hours with limitation of the resultant gangrene to minimal amounts in a significant percentage of cases. Finneran and Shumacker[43] similarly found this drug effective in reducing the incidence and extent of gangrene in the frostbitten feet and tails of rats. However, neither this drug nor stellate ganglionectomy were effective in the treatment of the frozen rabbit's ear. Frostbite of the dog's foot was benefitted by lumbar sympathectomy, especially in those animals which showed evidence of fairly pronounced vasomotor lability. Since high vascular tonus is thought possibly to be a predisposing factor in human frostbite, it is felt that interruption of sympathetic impulses might be more effective in the early treat-

TABLE V. RESULTS OF SYMPATHETIC BLOCKADE IN TREATMENT OF FROSTBITE

AUTHOR	SPECIES	EXTREMITY FROZEN	NUMBER	TEMPERATURE OF FREEZING (IN °C.)	DURATION FREEZING (IN MINUTES)	TREATMENT GIVEN	DETAILS OF TREATMENT	RESULTS		
								EXCELLENT	GOOD OR EXCELLENT	POOR
Crismon and Fuhrman, 1947	Rabbit	Ear	11	−55	1	No				11
			6	−55	1	Yes	Single stellate block			6
Fuhrman and Crismon, 1948	Rabbit	Ear	6	−55	1	No				6
			2	−55	1	Yes	Single stellate block 3 to 125 min. after injury			2
			4	−55	1	Yes	Single stellate block 3 to 125 min. after injury; repeated again next day			4
Lempke and Shumacker, 1949	Mouse	Tail	21	−15	5 sec.	No		1 (4.8)	6 (28.6)	15 (71.4)
			10	−15	5 sec.	Yes	TEAC 0.1 mg. q. hr. × 8, then q. 3 hr. × 16	3 (30)	7 (70)	3 (30)
Finneran and Shumacker, 1950	Rat	Tail	43	−15	5 sec.	No		4 (8.8)	6 (13.7)	37 (86.3)
			41	−15	5 sec.	Yes	TEAC 25 mg./kg. q. hr. × 8, then q. 4 hr. × 16	5 (12.1)	16 (37.9)	25 (62.1)
			41	−15	5 sec.	Yes	TEAC 25 mg./kg. q. hr. × 8, then q. 4 hr. × 16; started 1 hr. after injury	16 (37.9)	25 (62.3)	16 (37.7)
		Foot	22	−20	5 sec.	No		0	11 (50)	11 (50)
			47	−20	5 sec.	Yes	TEAC 25 mg./kg. q. hr. × 8, then q. 4 hr. × 16; started immediately	5 (10.6)	49 (93.5)	3 (6.5)
			43	−20	5 sec.	Yes	TEAC 25 mg./kg. q. hr. × 8, then q. 4 hr. × 16; started 1 hr. after injury	4 (9.3)	31 (72.1)	12 (27.9)

	Rabbit	Ear	39	−15	2	No		0	2 (5.1)	37 (94.9)
			8	−15	2	Yes	TEAC 25 mg./kg. q. hr. × 8, then q. 4 hr. × 16; begun immediately	0	0	8
			10	−15	2	Yes	Immediate stellate ganglionectomy	0	0	10
	Dog	Foot	20	−25	15	No		3 (15)	4 (20)	16 (80)
			20	−25	15	Yes	Immediate lumbar sympathectomy	7 (35)	9 (45)	11 (55)
Rödén, 1949	Rabbit	Foot	7	−15 to −40	2 to 33	No				
			7	−15 to −40	2 to 33	Yes	Periarterial injection of phenol 12 to 165 min. after injury	More edema and loss of tissue		
Arena, Gerbasi, and Blain, 1950	Rabbit	Leg	15	−10	30	No				15
			15	−10	30	Yes	25 to 50 mg./kg. TEAC q. 6 hr. until gangrene established or longer			15

TABLE VI. RESULTS FROM THE USE OF RUTIN IN THE TREATMENT OF FROSTBITE

AUTHOR	SPECIES	EXTREMITY FROZEN	NUMBER	TEMPERATURE OF FREEZING (IN ° C.)	DURATION FREEZING (IN MINUTES)	TREATMENT GIVEN	DETAILS OF TREATMENT	RESULTS		
								EXCELLENT	GOOD OR EXCELLENT	POOR
Fuhrman and Crismon, 1950	Rabbit	Ear	12	–55	1	No				12
			5	–55	1	Yes	50 mg./kg. q. d. 1 to 10 days before & 5 to 17 days after freezing			5
		Foot	16	–55	3	No			1	15
			6	–54 to –56	3	Yes	50 mg./kg. q. d. 1 to 10 days before & 5 to 17 days after freezing		4	2
			4	–54 to –56	3	Yes	100 mg./kg. q. d. for 3 days after freezing		3	1
Shumacker, Radigan, Ziperman, and Hughes, 1951	Mouse	Tail	64	–15	5 sec.	No		4 (6.3)	9 (14.1)	55 (85.9)
			40	–15	5 sec.	Yes	100 mg./kg. q. d. for 4 days after freezing	5 (12.5)	10 (25)	30 (75)
		Foot	20	–15	½	No		0	3 (15)	17 (85)
			20	–15	½	Yes	100 mg./kg. q. d. for 4 days after freezing	0	2 (10)	18 (90)
	Rat	Tail	15	–20	15 sec.	No		0	0	15
			15	–20	15 sec.	Yes	100 mg./kg. q. d. for 4 days after freezing	0	0	15
		Foot	42	–20	20 sec.	No		0	17 (40.5)	25 (59.5)
			43	–20	20 sec.	Yes	100 mg./kg. q. d. for 4 days after freezing	3 (6.9)	31 (72.1)	12 (27.9)
	Rabbit	Ear	22	–20	2	No		0	1 (4.5)	21 (95.5)
			14	–20	2	Yes	100 mg./kg. q. d. for 4 days after freezing	0	10 (71.4)	4 (28.6)
		Foot	21	–20	5	No		1 (4.8)	4 (19.9)	17 (80.9)
			12	–20	5	Yes	100 mg./kg. q. d. for 4 days after freezing	1 (8.3)	7 (58.3)	5 (41.7)

ment of human frostbite than in the treatment of animals which, by and large, exhibit a rather low vasomotor tonus. Arena, Gerbasi, and Blain[55] did not find tetraethylammonium chloride effective in limiting the gangrene of the rabbit's foot developing after frostbite.

There are a few clinical reports in the literature, made principally by French authors,[7, 18, 56, 57, 58] suggesting that the use of sympathetic blocks early in the treatment of frostbite may be very effective. It is difficult to evaluate this treatment from the few experiences recorded and obviously more experience is desirable for settling this question. For one thing, treatment in the reported cases has often been delayed too long after injury until gangrene was already evident. The senior author has had a modest experience with the use of operative sympathetic denervation in the treatment of some of the late sequelae of frostbite. There can be no doubt but that such treatment is of great benefit, especially in alleviating evidences of persistent sympathetic overactivity and in relieving sensitivity to cold, as well as in facilitating the healing of indolent ulcers. He has had only scant experience with the use of operative sympathectomy in the early treatment of frostbite. In a few cases operations performed within the first week after the cold injury and during the phase of hyperemia seemed clearly to decrease significantly the spontaneous pain and sensitivity of the foot to touch. The procedure also seemed to hasten the subsidence of edema. One could only speculate as to whether the procedure had any effect in limiting the extent of loss of tissue. Although in some animal experiments the use of the autonomic blocking agents seemed to decrease the resultant gangrene, it would not appear logical to use these agents in treating frostbite in man, since they have proved so unreliable in bringing about vasodilatation of the extremities, particularly in the presence of marked vasospasm.[59, 60, 61, 62]

Rutin.—Vitamin P-like substances, of which rutin is an example, have been reported to reduce capillary permeability as well as fragility.[63] Because increased capillary permeability is a prominent feature of frostbite and because they felt that they had shown control of edema by mechanical means was effective in preventing gangrene, Fuhrman and Crismon[49] treated frostbite of the rabbit's ear by use of this drug. Microscopic study of the circulation following frostbite of previously treated rabbits revealed a delay of stasis but there was no reduction in the degree of gangrene—results similar to those obtained after stellate block. Gangrene was not prevented in the ears of five rabbits treated with rutin both before and after freezing (Table VI). Rutin administered before and/or after frostbite of the feet of rabbits was, however, effective in limiting the extent of gangrene. The prevention of tissue loss in those animals in which the drug was given only after injury suggested that rutin did not inhibit the primary leakage from, and stasis in, the true capillaries but prevented the extension of vascular occlusion which is ordinarily not complete until about fifty hours after freezing. Shumacker and his associates[39] obtained varied results from the administration of rutin to several species of animals. The degree of gangrene of the feet of rabbits and rats, and ears of rabbits was reduced to a significant extent. No effect was noted in the case of the tails of rats or mice or the feet

TABLE VII. RESULTS FROM THE USE OF ANTIHISTAMINICS IN TREATMENT OF FROSTBITE

AUTHOR	SPECIES	EXTREMITY FROZEN	NUMBER	TEMPERATURE OF FREEZING (IN ° C.)	DURATION FREEZING (IN MINUTES)	TREATMENT GIVEN	DETAILS OF TREATMENT	RESULTS		
								EXCELLENT	GOOD OR EXCELLENT	POOR
								Reaction graded 1, 2, 3		
								1	2	3
Macht, Bader, and Mead, 1949	Man	Spot on arm	12	–40	10 sec.	No		0	1	11
			12	–40	10 sec.	Yes	Saline iontophoresis	0	2	10
			12	–40	10 sec.	Yes	Benadryl iontophoresis	10	1	1
			12	–40	10 sec.	Yes	Pyribenzamine iontophoresis	11	1	0
Shumacker, Radigan, Ziperman, and Hughes, 1951	Mouse	Tail	64	–15	5 sec.	No		4 (6.3)	9 (14.1)	55 (85.9)
			32	–15	5 sec.	Yes	Benadryl 0.43 mg./kg. q. 6 hr. × 5	2 (6.3)	4 (12.5)	28 (87.5)
		Foot	20	–15	½	No		0	3 (15)	17 (85)
			20	–15	½	Yes	Benadryl 0.43 mg./kg. q. 6 hr. × 5	0	2 (10)	18 (90)
	Rat	Tail	15	–20	15 sec.	No		0	0	15
			17	–20	15 sec.	Yes	Benadryl 0.43 mg./kg. q. 6 hr. × 5	0	2	15
		Foot	42	–20	20 sec.	No		0	17 (40.5)	25 (59.5)
			20	–20	20 sec.	Yes	Benadryl 0.43 mg./kg. q. 6 hr. × 5	2 (10)	16 (80)	4 (20)
	Rabbit	Ear	22	–20	2	No		0	1 (4.5)	21 (95.5)
			18	–20	2	Yes	Benadryl 0.43 mg./kg. q. 6 hr. × 5	0	5 (27.8)	13 (72.2)
		Foot	21	–20	5	No		1 (4.8)	4 (19.1)	17 (80.9)
			12	–20	5	Yes	Benadryl 0.43 mg./kg. q. 6 hr. × 5	3 (25)	8 (66.7)	4 (33.3)
								Healed	"Scarred"	Gangrene
Frommel and Piquet, 1946	Guinea Pig	Both legs	6	?	?	No		2	1	3
			8	?	?	Yes	Antergan 10 mg./kg. q. d. × 12, then 20 mg./kg. × 6	5	3	0

of mice. However, in these particular experiments the injury to the tails of rats was so severe that not even rapid thawing was effective. While rutin is not as beneficial as other methods of treatment, it apparently has some effect in reducing tissue necrosis, presumably on the basis of inhibition of stasis.

Antihistaminic Drugs.—Lewis[5] advanced the theory that the vascular reaction following thawing was due to the liberation of a histamine-like substance or substances from the cells injured by cold or ischemia. The advent of the antihistaminic drugs, therefore, offered a new possibility in the treatment of frostbite. Frommel and Piquet[64] in 1946 treated frostbite of the legs of guinea pigs with Antergan with a resultant decrease in the amount of gangrene as compared with that observed in similarly injured untreated animals. They also reported more rapid healing and less scarring in the treated group. Macht[65] and his associates froze several small areas on the extremities of human volunteers. Some of these areas of skin had received no previous treatment, while others had been subjected to iontophoresis with saline, Benadryl, or Pyribenzamine one hour before exposure. The areas treated with the antihistaminic drugs developed fewer vesicles and wheals which were delayed in appearance and less severe when they did form (Table VII).

The intraperitoneal injection of Benadryl following frostbite was evaluated by Shumacker and his colleagues[39] in mice, rats and rabbits. The results were rather similar to those obtained following treatment with rutin, in that extensive gangrene was significantly reduced in the feet of rats and rabbits and the ears of rabbits. Though these results were not dramatic, they suggested that the antihistaminic drugs might be a useful adjuvant in the treatment of frostbite.

Combination of Therapeutic Measures.—Since a number of the measures previously discussed have been shown to be effective in reducing the incidence and extent of gangrene following frostbite, the question naturally arises whether a combination of some of these measures might be even more effective. The combination of immediate rapid thawing of the frozen part and the use of tetraethylammonium chloride in order to block sympathetic impulses was investigated by Lempke and Shumacker.[36] The frostbitten tails of mice so treated developed less gangrene than when either method of treatment was used alone. When these experiments were repeated by Finneran and Shumacker[43] no significant difference was found in the case of frostbite of the rat's tail or feet. Rapid thawing and immediate sympathetic denervation similarly did not alter the result significantly in the case of frostbite of the rabbit's ear. Rapid thawing and immediate sympathetic denervation in the case of frostbite of the dog's foot, however, appeared to give improved results as compared with either method of treatment alone, though the numbers treated were too few to have clear statistical significance.

Crismon and Fuhrman[29] applied plastic casts and pressure dressings to frozen feet of rabbits following rapid thawing without improvement in the result over that obtained from rapid thawing alone except that there was some reduction in late scarring.

When Finneran and Shumacker[43] studied the effect of rapid thawing and heparinization, they found no significant difference in the end results of frostbite of the rat's foot and tail as compared with those obtained with rapid thawing alone, though there was a significant improvement over those obtained with the use of heparin alone. In a few animals, Lange and Boyd[27] and Fuhrman and Crismon[49] tried the effect of heparinization and pressure dressings. Both studies, however, involved one or two animals and the results are inconclusive. However, they demonstrated no advantage over the use of heparin alone.

SUMMARY AND CONCLUSIONS

From this review of the available experimental data several conclusions may be safely drawn. In the first place, and it is of great importance clinically, there is no credible evidence to suggest that the frostbitten extremity should be thawed slowly or that there is any advantage whatsoever in the use of measures to keep the extremity cool or cold for either a brief or a prolonged period of time. The majority of studies indicate clearly that the treatment of frostbite with cold either of long or short duration is not beneficial and indeed may be harmful. The single report suggesting that slight benefit from cooling may ensue is subject to obvious question because it involves the treatment of only six feet of rabbits and such treatment was carried out in conjunction with the application of plastic casts.

The use of pressure dressings and plaster casts would also seem to be contraindicated. The two studies of sufficient thoroughness to warrant conclusions are unfortunately contradictory. However, the only study in which a very large number of animals was used and several species were studied indicated that such treatment was of no value and might be harmful.

The proponents of these two methods of treatment base their suggestions upon the belief that edema is the significant factor in the production of gangrene following frostbite. One attempts to prevent its development by slowly warming the frozen part, while the other attempts to control it mechanically. The superiority of immediate rapid warming of the frozen extremity as the most effective single therapeutic measure in preventing subsequent gangrene refutes the former idea. The latter is certainly placed in serious doubt, not only by the observation that such mechanical measures actually do not improve the results in experimental frostbite, but also by the fact that certain measures of remarkable efficacy, such as rapid thawing, are not associated with less edematous swelling of the frozen part. There is a great deal of experimental data based upon observations in a variety of species and in frostbite of different portions of the body which show rapid thawing to be extremely effective in preventing loss of tissue. Indeed, all of the experiments reported are in agreement in this respect except for one, details of which are not given in the published report. Studies inquiring into the mode of action of this method of treatment indicate that benefit is derived from it in all probability as a result of the shortening of the duration during which the part is actually frozen and prompt induction of good blood flow with vasodilatation and inhibition of capillary stasis.

Efforts to produce vasodilatation by blocking the sympathetic impulses to the frozen extremity have given varying experimental results. In one study no ultimate benefit was observed in treating twelve rabbits with frozen ears by one or two stellate blocks with procaine. In another study the use of repeated administration of tetraethylammonium chloride did not bring about any improvement in frostbite of the rabbit's foot. In other studies, however, the use of tetraethylammonium chloride appeared to result in decrease of tissue loss after frostbite of the tails and feet of mice and rats. Sympathectomy was somewhat helpful in reducing the extent and incidence of gangrene in the case of frostbite of the dog's foot and seemed more definitely beneficial when combined with rapid thawing. Sympathetic denervation was not found to be effective in the case of frostbite of the rabbit's ear. While the results thus far reported are variable, they at least demonstrate conclusively that no harm results from sympathetic interruption as had been predicted would be the case by a number of authors on theoretical grounds.

Experimental results with the treatment of frostbite by heparinization have also been conflicting. They vary from studies which would indicate that heparinization is without any value whatsoever to experimental observations which seem to demonstrate that heparin has remarkable efficacy in the prevention of gangrene. Altogether, taking into consideration control of the anticoagulant effect in the various studies, it would seem fair to conclude that intensive anticoagulant therapy is of benefit in the prevention of necrosis after frostbite.

A few additional methods of treatment have been shown to have moderate efficacy in certain species of animals, though they were not found to be effective in diminishing gangrene after frostbite in all species studied. One utilizes antihistaminic agents in an effort to inhibit the activity of histamine-like substances which presumably might contribute to capillary injury, hyperpermeability and stasis. The other utilizes rutin in an effort to reduce capillary permeability and stasis.

It is unfortunate that these various methods of treatment have as yet been subjected to little or no controlled clinical experimentation. It is felt from the experimental data that there is every reason to abandon the use of local chilling of the frozen part and efforts to bring about slow thawing and that, instead, the frozen part should be thawed as rapidly as possible, taking care to use temperatures only slightly above body temperature. It is recognized that the conditions under which frostbite occurs present difficulties in the application of this, the single most effective method of treatment. Such difficulties are obviously not insurmountable. It would appear worth while for the armed forces, in which the problem of frostbite is very great indeed, to carry out studies designed to see what measures—practical and applicable to troops in combat—could be put into effect. In spite of the conflicting experimental studies it seems advisable to use anticoagulant therapy in all cases of moderate or severe frostbite provided, of course, that there are no other specific contraindications to this method of treatment. Since, however, there are no controlled observations of human frostbite,

it would appear desirable to study further the efficacy of this method of treatment by applying it to matched alternate cases. In spite of the varying results which have been obtained experimentally, it is also suggested that interruption of sympathetic impulses to the frozen extremity may be of some benefit. It is certainly evident that there is no basis for the supposition that such treatment would be harmful. The question can be answered only by controlled observations of the treatment of frostbite in man. Due to the variable results which have been shown to obtain with the use of autonomic blocking agents in cases of impaired circulation, it would not be wise to use these agents in an effort to block sympathetic impulses. Instead, repeated procaine sympathetic blocks, or better still, continuous sympathetic blocks with an in-lying catheter in the paravertebral area and operative sympathectomy in selected instances of severe frostbite should be employed. Difficulties of evaluation of results would be lessened if such measures were carried out unilaterally in cases of apparently equal bilateral injury. Experimental data are sufficiently suggestive also to warrant the clinical trial of rutin and of antihistaminic agents. The use of pressure dressings would seem to have no place in the treatment of frostbite. It must be always kept in mind that evaluation of the various methods of treatment in human frostbite presents many difficulties, and that every effort should be made in such studies to obtain as adequate control as is possible.

In this discussion we have not dealt with certain other measures in the treatment of frostbite which are obviously of the greatest importance. They include every effort to keep the frozen extremity clean, to protect it from injury and infection, to keep the extremity with impaired circulation in the optimal position of blood flow, to carry out careful débridement, removing dead tissue through the line of demarcation and to conserve all viable tissue possible. Obviously, every attention must be given to such measures, regardless of any other specific treatment which may be used.

Though there are many gaps in our knowledge concerning the functional pathology of frostbite and its best treatment, considerable progress has been made. It appears that we are now in a position to handle these trying problems in a reasonably intelligent fashion. Furthermore, the type of clinical investigation which is so badly needed appears to be clearly outlined. Finally, certain widely accepted concepts based almost entirely upon armchair philosophy of the past have been shown to be erroneous and can be discarded.

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Surgical History

CONDUCTED BY JOHN R. PAINE, M.D.

EARLY HISTORICAL ASPECTS OF APPENDICITIS

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APPENDICITIS is a common disease. It is probable that everyone has some acquaintance with it and knows something about its treatment. There is a certain pleasure, and perhaps some immediate value, in tracing the ideas which have led to our present conception of the disease, which was done in considerable detail by Latimer[25] and by Sprengel[52, 53] in the early part of this century. It is because these excellent reviews are almost unknown to the present medical generation that the author has felt justified in offering another survey of the historical aspects of appendicitis.

The history of appendicitis can be divided into two eras: before and after the appearance of Reginald Fitz's epochal paper, "Perforating Ulcer of the Vermiform Appendix, With Special Reference to Its Early Diagnosis and Treatment."[13] Before Fitz, appendicitis was thought to be a rare lesion, worthy of single case reports. A few years after his article appeared, series of 100 or more cases became common in medical literature, and today appendectomy is perhaps the most common abdominal operation.

The vermiform appendix was first described by Jacob Berengario da Carpi[6] (1470-1530). Its physiologic function remains unknown. Absence of the appendix in many species was noted by early comparative anatomists, and both Portal[44] and Morgagni[37] removed the appendix from experimental animals without discernible effect. Mestivier,[35] in 1759, seems to have been the first to recognize the organ as a site of disease, although Ruysch[48] is said to have described finding a needle in the appendix in 1691, and Saracenus[50] is said to have described and incised an appendiceal abscess in 1642. Mestivier described the case of a man suffering from a fluctuant tumor in the right side of the abdomen, which yielded pus upon incision. Although the wound healed, the patient eventually succumbed, and at autopsy the cecum was seen to be covered with gangrenous patches and the appendix contained a rusty pin. Mestivier concluded that the irritation set up by the pin was responsible for the inflammatory reaction seen in the cecum and the localized peritonitis. Several case reports appeared in the next half-century describing various foreign bodies found within the appendix, although the authors did not consider these to be causes of death. Hevin[19] stated that he had found bird shot in the appendix of patients who were fanciers of wild fowl.

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In 1812 Parkinson[43] reported the death of a five-year-old boy, following two days of illness marked by vomiting, prostration, and a tender, distended abdomen. Necropsy demonstrated acute generalized peritonitis with a perforated appendix as the sole visceral lesion. Although it is not so stated in the report, it seems obvious that the author recognized this perforation as the cause of death. This appears to be the first time that perforation of the appendix was considered a lethal factor.

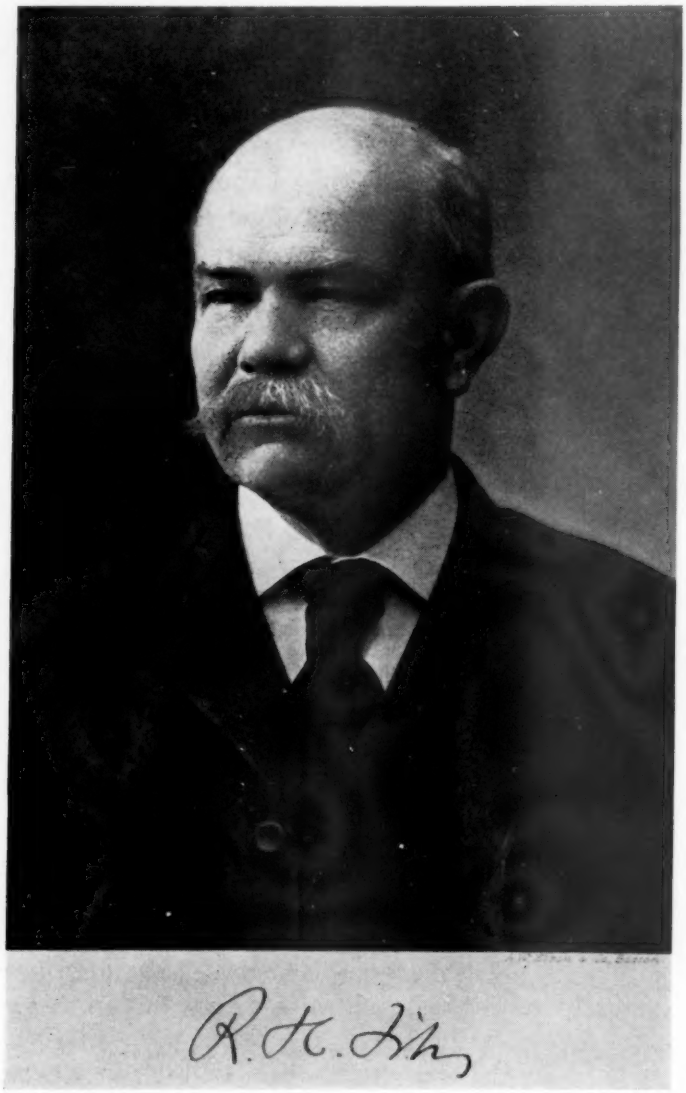
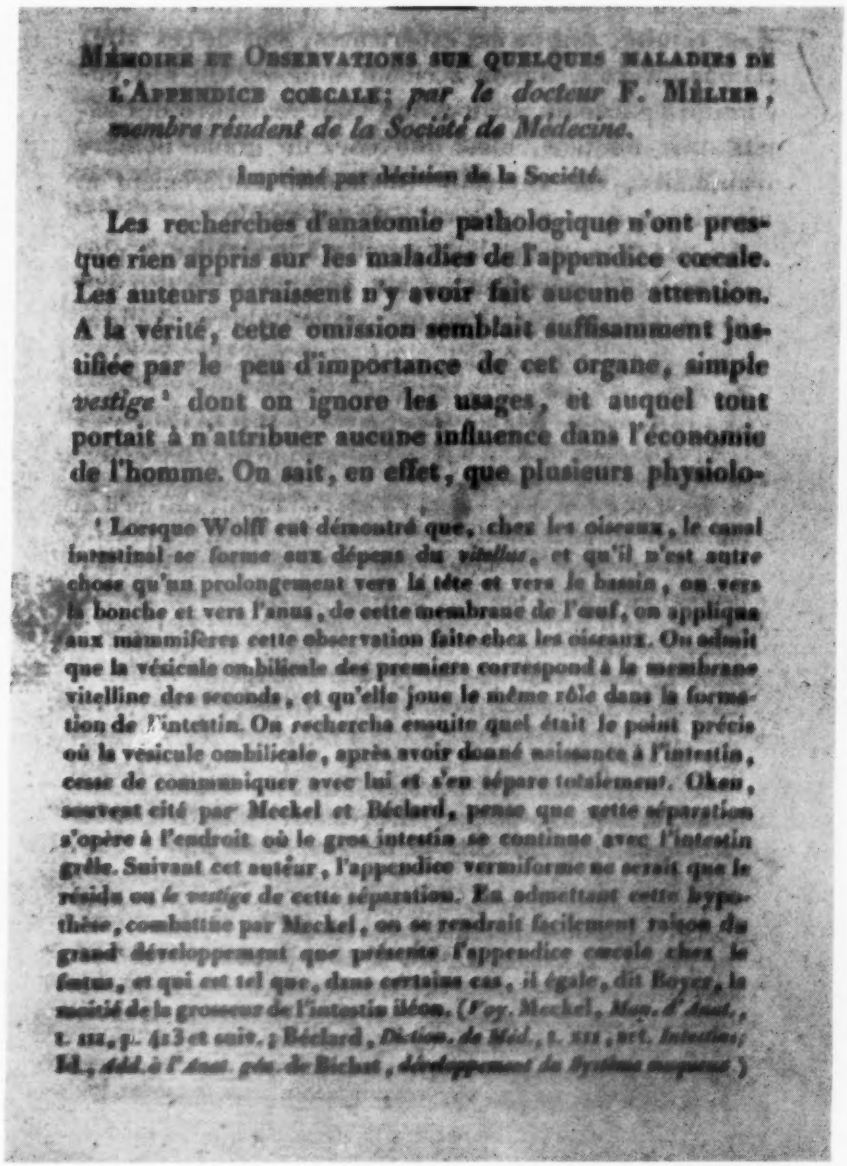


Fig. 1.—Engraving of Dr. Fitz, obtained through the courtesy of Dr. Reginald Fitz and The Shattuck Medical Library of the Harvard Medical School.

Disease of the appendix was first considered a specific entity by Louyer-Villermay in a paper published in 1824 entitled, "Observations pour servir a la histoire des inflammations de l'appendice cecale."[28] He reported two case histories consistent with our ideas of acute appendicitis, wherein gangrenous

appendicitis was demonstrated at autopsy. The author unhesitatingly condemned the appendix as the cause of death, although he was somewhat puzzled about the absence of generalized peritonitis.



MÉMOIRE ET OBSERVATIONS SUR QUELQUES MALADIES DE L'APPENDICE CŒCALE; *par le docteur* F. MÉLIER, *membre résident de la Société de Médecine.*

Imprimé par décision de la Société.

Les recherches d'anatomie pathologique n'ont presque rien appris sur les maladies de l'appendice cœcale. Les auteurs paraissent n'y avoir fait aucune attention. A la vérité, cette omission semblait suffisamment justifiée par le peu d'importance de cet organe, simple *vestige*[1] dont on ignore les usages, et auquel tout portait à n'attribuer aucune influence dans l'économie de l'homme. On sait, en effet, que plusieurs physiolo-

[1] Lorsque Wolff eut démontré que, chez les oiseaux, le canal intestinal se forme aux dépens du *vitellus*, et qu'il n'est autre chose qu'un prolongement vers la tête et vers le bassin, ou vers la bouche et vers l'anus, de cette membrane de l'œuf, on appliqua aux mammifères cette observation faite chez les oiseaux. On admit que la vésicule ombilicale des premiers correspond à la membrane vitelline des seconds, et qu'elle joue le même rôle dans la formation de l'intestin. On rechercha ensuite quel était le point précis où la vésicule ombilicale, après avoir donné naissance à l'intestin, cesse de communiquer avec lui et s'en sépare totalement. Oken, souvent cité par Meckel et Béclard, pense que cette séparation s'opère à l'endroit où le gros intestin se continue avec l'intestin grêle. Suivant cet auteur, l'appendice vermiforme ne serait que le résidu ou le vestige de cette séparation. En admettant cette hypothèse, combattue par Meckel, on se rendrait facilement raison du grand développement que présente l'appendice cœcale chez le fœtus, et qui est tel que, dans certains cas, il égale, dit Boyer, la moitié de la grosseur de l'intestin iléon. (*Voy.* Meckel, *Man. d'Anat.*, t. III, p. 413 et suiv.; Béclard, *Diction. de Méd.*, t. III, art. *Intestins*; Id., *Add. à l'Anat. gén. de Bichat, développement du système muqueux.*)

Fig. 2.—Facsimile of Mélier's paper, "Memoirs and Observations on Some Diseases of the Cecal Appendix."

Three years later, Mélier published an article which Kelly and Hurdon[22] consider the most significant in the pre-Fitz era: "Mémoire et observations sur quelques maladies de l'appendice cecale."[33] Like the work of other scientists too far in advance of their times, Mélier's and Louyer-Villermay's theses were destined for temporary obscurity. According to Trotter,[55] "the

successful shepherd thinks like his sheep, and can lead his flock only if he keeps no more than the shortest distance in advance. . . . Variations from the normal standard in intellectual matters are tolerated if they are not very conspicuous, for man has never yet taken reason very seriously." Martens's[29] hypothesis concerning infectious disease and tuberculosis in particular was lost from 1720 until 1911 when it was disinterred by Singer. Mélier noted the comparative lack of knowledge of lesions of the appendix, but cited several recent publications, notably Louyer-Villermay's, as indicating that disease of this organ might be of grave consequence. He then reported a case in which a patient recovering from an illness (which we would consider appendicitis) took an enema, had a return of severe abdominal pain, and died in eighteen hours with the clinical picture of peritonitis. At autopsy there was seen generalized peritonitis with a gangrenous, perforated appendix. Certainly this combination of generalized peritonitis with a gangrenous or perforated appendix must have been observed previously, but Mélier was the first to insist that the appendix was the source of the peritonitis, rather than the site of concomitant disease. "I believe that fecal matter accumulated in the appendix, which gradually became inflamed, gangrenous, and finally perforated. The early symptoms, colic-like, represent inflammation and distention of the appendix; its rupture was in turn responsible for the peritonitis." He further opined that the enema hastened or produced the perforation; an opinion reminiscent of our contemporary antipurgation program. Four similar cases were reported, and he credited Sevestre with the correct premortem diagnosis in the second case. This was undoubtedly the first diagnosis, correct or otherwise, of perforation of the appendix, and it was made because of the clinical similarity to Mélier's first case. According to Kelly and Hurdon, Mélier further suggested that, if the diagnosis could be established with regularity, operative treatment might be considered. I have not been able to confirm this statement in Mélier's original paper, even by inference.

It has been conceded generally that Dupuytren's[9] failure to recognize the validity of Mélier's thesis retarded the diagnosis and treatment of appendicitis for decades. Mondor,[36] in a recent biography of Dupuytren, writes that it is a source of great sorrow to surgeons even today that the discovery of appendicitis was within Dupuytren's reach, only to be discarded. His sole reference to this problem appears in his "Lecons chirurgicales" where, in a discussion of tumors of the right iliac fossa he states that the predominance of abscesses in the right lower quadrant was due to anatomic and physiologic differences in the right and left colon, favoring stagnation in the cecum and consequent disease. He did admit disease of the appendix existing as a rare entity, but denied Mélier's contention of causal relationship between the diseased appendix and the relatively common inflammatory right iliac tumors. It has been said that Dupuytren's opposition to Mélier was extremely active. For example, Meiling[32] stated, "Historically, we are familiar with the young French surgeon, Mélier's, attempt to guide the surgical approach to the treatment of inflammation of the vermiform process, only to have the great

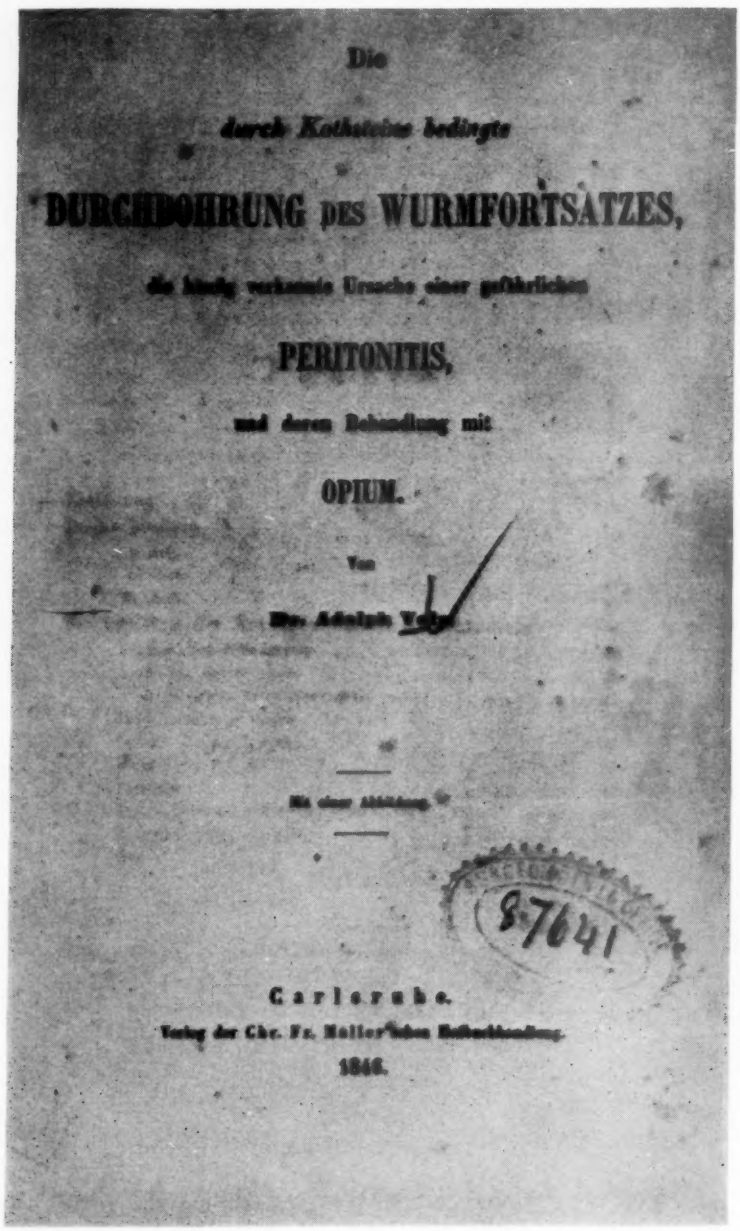
Dupuytren thwart and crush his efforts." If he did take an active role in opposition to Mélier's hypothesis, it was through his pupils and associates, as I have been unable to find any further reference to the problem from the pen of Dupuytren himself. To be sure, his associates, Ménière,[34] Husson and Dance[21] took violent exception to Mélier's views. Ménière[34] described instances of generalized peritonitis to validate the Dupuytren theory, and overlooked the presence of a perforated or gangrenous appendix described in the same protocol. Sprengel attempted to explain the opposition to Mélier by assuming that the disease was seen in different stages by the pathologist and the surgeon. He suggested the cases usually seen, and occasionally drained, by Dupuytren, represented well-localized abscesses for the most part, whereas the cases of peritonitis were seen at autopsy by Mélier.

There is reason to suspect, however, that Mélier himself was not entirely aware of the significance of his work. Shortly after the publication of his paper he became intensely interested in public health, and devoted the remainder of his life to this field. His later publications over a thirty-year period were devoted entirely to industrial and governmental medicine. Though he is said to have been active in the practice of medicine during this period, he published no further clinical material. The conception of primary cecal disease was current for many years and was responsible for the term "perityphlitis" introduced by Goldbeck[14] in 1830, and "typhlitis," suggested by Albers[1] a few years later. During the next few decades a considerable amount of attention was given to the syndrome which we now recognize as appendicitis. The descriptions of signs and symptoms were excellent, but with few exceptions the cecum and pericecal tissues were considered the sources of disease.

Thomas Hodgkin,[20] in 1836, and Bright and Addison,[4] in 1839, recognized the vermiform appendix as the most common source of disease in the right iliac fossa. Bright and Addison devoted six pages of the "Elements of the Practice of Medicine" to inflammation of the cecum and vermiform appendix. The names Hodgkin, Bright, and Addison are familiar to every student of medicine, but their part in the development of the concept of appendicitis has been overshadowed by the diseases bearing their names. The ever-necessary admonition toward gentleness in examination appears in Bright and Addison: "At the same time we must endeavor to disturb the part as little as possible, for the contents of the intestine or of the abscess may become extravasated into the peritoneal cavity, if violence is done in our manual examination."

The most significant German contribution was Voltz's "Perforation of the Appendix by Fecaliths, a Frequent Cause of Peritonitis; Its Treatment With Opium."[56] The role of the appendix was clearly demonstrated in thirty-eight cases followed to autopsy, although undue importance was given to the part played by fecaliths. Voltz stressed the importance of rest for the intestinal tract as produced by opium, and presented an amusing parallel between the contemporary treatment of peritonitis and the treatment of fracture:

If fractures were treated as is peritonitis: a healthy man falls, feels pain in his foot and is unable to stand or walk. Without recognizing the cause, his physician reasons that while he was walking he had no pain. Forthwith he is made to stand and is held on his feet, with the result that the pain increases and he is still unable to walk. Again, a healthy man following bodily exertion has a pain in the abdomen which is followed by constipation. Again, without knowledge of the cause, his physician reasons that when he had no constipation he had no pain. Ergo: catharsis. Result: pain is increased and the bowels are still inactive. On the other hand, if the fracture is splinted and the bowel is splinted by opium:


Die

durch Kothsteine bedingte

DURCHBOHRUNG DES WURMFORTSATZES,

die häufig verkannte Ursache einer gefährlichen

PERITONITIS,

und deren Behandlung mit

OPIUM.

Von

Dr. Adolph Voltz

Mit einer Abbildung.

8-7641

Carlsruhe.

Verlag der Chr. Fr. Müller'schen Buchhandlung.

1846.

Fig. 3.—Title page of Voltz's paper, "Perforation of the Appendix Caused by Fecaliths, a Frequent Source of Dangerous Peritonitis, and the Treatment with Opium."

> after the fall the physician recognizes the disability as a fracture and immobilizes the patient by splinting and bed rest. In time the pain goes away and the patient leaves his bed voluntarily. The case of constipation is considered as peritonitis due to bowel perforation and the physician orders medication to further constipate, i.e., opium. While this medication is in use the pain goes away and peristalsis returns. The patient requests a bed pan without using a purgative. May the time come when we use drugs for disease as intelligently as we use splints for fractures.

Voltz felt that the incidence of peritonitis of unknown origin was inversely proportional to the attention paid to the appendix at autopsy. He reported thirty-eight cases treated by the customary antiphlogistic method with one recovery, and eight cases treated by opium with eight recoveries. Graves and Stokes are credited with the first use of opium without bloodletting.

The first important American work on appendiceal disease was published in 1856 by Lewis: "A Statistical Contribution to Our Knowledge of Abscess and Other Diseases Consequent Upon the Lodgement of Foreign Bodies in the Vermiform Appendix, With a Table of Forty Cases."[27] He summarized the contemporary knowledge and from his own experience gave a concise picture of appendicitis in a stage which we would consider to be very late in the disease. It must be recognized that the picture of early acute appendicitis recognized today by the intelligent layman was then obscured by the frequently fatal inflammatory tumor of the right lower quadrant—appendicitis in a very late stage. Three of the cases reported by Lewis recovered.

Gradually the appendix came to be recognized as the source of so-called "perityphlitis" and in the early eighties, Matterstock,[30] With,[59] and Fenwick[11] had separately pointed to this causal relationship, absolving the cecum as the primary site of disease. Generally, with the exception of Hancock,[16] Parker,[42] and Bull,[5] therapy remained nonoperative until the appearance of the epochal essay of Reginald Fitz.

Fitz and appendicitis are inseparable, since Fitz not only described the disease, but in addition coined its name. This was done to emphasize his indictment of the appendix as the cause of a host of diseases variously called typhlitis, perityphlitis, paratyphlitis, tuphlo-enteritis, cecitis, "inflammation of the bowels," and ileo-cecal abscess, to mention but a few of the names. His article, "Perforating Ulcer of the Veriform Appendix, With Special Reference to Its Early Diagnosis and Treatment," brought into clear focus the accumulated information and established once and for all the origin of the great majority of diseases arising in the right iliac fossa. Operation, rare in the past, was suggested as the most promising therapy.

> If, after the first 24 hours from the onset of severe pain, the peritonitis is evidently spreading and the condition of the patient is grave, the question should be entertained of an immediate opening for exposing the appendix and determining its condition with reference to its removal. If any good result is to arise from such treatment, it must be applied early.

Concluding, Fitz says:

> The vital importance of early recognition of early peritonitis is unmistakable.
>
> Its diagnosis in most cases is comparatively easy.
>
> Its eventual treatment by laparotomy is generally indispensable.
>
> Urgent symptoms demand immediate exposure of the appendix, after recovery from the shock, and its after-treatment according to surgical principles.
>
> If delay seems warranted, the resulting abscess, as a rule intraperitoneal, should be incised as soon as it becomes evident. This is usually on the third day after the appearance of the characteristic symptoms of the disease.

Fitz brought appendicitis from the status of a curiosity to an everyday disease and opened the way for early surgical intervention.

Because of Fitz, appendicitis ceased to be a medical curiosity and became an everyday disease. J. M. T. Finney[12] told of being the subject of a consultation by Fitz.

> While I was still a medical student I had been taken with a pain in my abdomen. Dr. Tarbell, in whose house my Aunt Lizzie and I had rooms, had been called in. After looking me over, he had said, 'It looks to me, John, as if you had a case of Fitz' disease (the name he gave to appendicitis), and if you are not better in the morning I shall ask Fitz to see you.' My abdomen was still feeling pretty painful the next morning, so Dr. Fitz was called in. He saw me, poked me over and said to Dr. Tarbell, 'Yes, this is a case of appendicitis, and if he isn't better very soon you had better call in Dr. Porter.' . . . I confess to a secret feeling of satisfaction ever since that I had been honored by having Dr. Fitz poke over my abdomen and make a diagnosis of appendicitis in the very year, 1886, that his paper on appendicitis was published.

Within a few years after the appearance of Fitz's paper, the story of appendicitis had become almost entirely surgical in character. Previously there had been occasional reports of surgical intervention specifically for appendiceal abscess. Hancock's[16] procedure differed from the drainage of the right iliac abscess insofar as he intervened before the onset of fluctuation to attack the mass itself. Willard Parker,[42] in 1867, published a report of four cases in which appendiceal abscesses had been drained. The first operation had been performed one year after Hancock's. It is not certain whether he was familiar with the latter's report at the time. Parker suggested that the incision be carried out sometime between the fifth and twelfth day of the disease, i.e., after the abscess had walled off and before it ruptured or diffused into the general peritoneal cavity. It is said that for many years this procedure was known in the United States as the Willard Parker operation. A number of case reports followed Parker's until the incision of an appendiceal abscess ceased to be a seven-day wonder.

Kronlein[23] is credited with the first formal appendectomy, which was performed in 1884, after a tentative diagnosis of peritonitis due to perforation of the appendix had been made. The patient survived the procedure, but died of his peritonitis three days later. Kronlein had been strongly influenced by Mieulicz's work on perforation of the intestinal tract and the possibilities of cure if the perforation could be closed. Hall,[15] in 1886, removed a perforated

appendix from a hernial sac, and Morton,[39] eight months earlier, had removed the major portion of a perforated appendix, leaving in situ small portions of the tip and the base. Sands,[49] in 1887, made the diagnosis of perforation of the appendix and successfully sutured the perforation. At about the same time Treves[54] made the diagnosis of appendiceal disease, advised operation during the quiescent period, and at operation, which was planned as an appendectomy, "was able to correct the distortion of the appendix without removing it." While the procedures of Sands and Treves may seem absurd today, they represented formal attack upon the immediate source of appendiceal disease as it was then understood.

With planned appendectomy, the surgery of appendicitis moved into the modern era. Many factors contributed to the progress from the different incision of a fluctuating mass in the right lower quadrant, through the incision before fluctuation of Willard Parker, to planned appendectomy. Anesthesia had made deliberate surgery possible; antisepsis, later asepsis, had made invasion of the peritoneal cavity safe; and the careful analysis of clinical histories and autopsy findings had made accurate diagnosis possible. Appendicitis, like the poor, had always been with us, but we knew it not. In this connection, Short[51] recently presented some interesting evidence to the effect that, while appendicitis may have been present since the beginning of man, its incidence has increased remarkably in the last century.

The major problem remaining concerned the proper timing of operation. For a considerable period of time, the initial attack, unless severe, was considered the province of the internist. If the attack increased in severity, or if the attacks became frequent, the surgeon came into his own, and the cry of "too late" began to appear in the literature. Bull,[5] in 1888, declared that mortality would not be lowered until operation was performed before the onset of generalized peritonitis. In the following year, Dennis[8] came out for operation during the first twenty-four to forty-eight hours of the first attack. At this time many physicians felt that it was safer to operate after the successful termination of the attack, when the patient had fully recovered; the so-called interval operation. Dennis felt it unsurgical to recommend this in all recurrent cases, as the danger incident to appendectomy was as great or greater than danger of recurrence. Richardson,[46] in 1899, came to conclusions which are equally valid today. He felt that early (up to forty-eight hours) was advisable; that the value of operation was questionable if peritonitis was localizing and the patient improving, or if the patient's condition was too critical to withstand the operative insult; that the appendix should not be removed in the presence of a well-localized abscess; and that the appendix should be removed during a free interval if necessary. This paper was discussed by John B. Deaver,[7] who felt that the preferable time for operation was within the first few hours, and that all cases should be operated except in the presence of acute generalized peritonitis and collapse. The concept of early operation became generally accepted in the United States and has continued as standard practice.

Opinion was much more conservative on the Continent, particularly in Germany. The treatment of appendicitis was one of the major topics, for the first time, at the German Surgical Congress in 1901. Sonnenburg was considered one of the leading German authorities, and Muhsam,[40] speaking for him, made the following recommendations:

1. Operation in the free interval.
2. Appendicitis simplex is seldom an indication for operation, and then only in the presence of an empyema.
3. In the presence of perforation, operation should be carried out in selected cases.
4. Early operation for gangrenous appendicitis.
5. Gangrenous and perforated appendices with complications must be operated upon.

In the discussion Kummel[24] was also conservative in his recommendations for the acute stages, but recommended immediate operation upon the moribund. Sprengel,[53] in another paper, defended early (within forty-eight hours of onset) operation. This viewpoint was concurred in by Rehn,[45] but was opposed by the majority of the discussers. At an earlier Congress, one of the speakers stated that he was hardly in a position to discuss "early" operation, as in his experience the mass did not appear before the fourth or fifth day.

The controversy about early operation gradually decreased in intensity, and by 1910 the value of early intervention was generally recognized throughout the surgical world. In remote communities this was not always true. Blaskowitz states that in his native city in Roumania, the first operation for acute appendicitis was performed in 1915. The tendency to minimize the danger of appendicitis, even in the United States, can be demonstrated from the analysis of any large series of appendicitis fatalities.

As late as 1940 occasional protests against routine early operation could be found in the literature. Oldfield[41] stated: "I have so far not had a case (appendicitis) that has needed operation, though I do not imply that an operation is never needed." His suggested routine included an enema, fasting, fluids, the use of a mixture of castor oil and olive oils, and rest. Williams[58] agreed that timely doses of castor oil would avert acute appendicitis. These views concur with those of Berry,[3] as published in 1932. It is difficult to explain the occasional recrudescence of the nonoperative therapy in the face of the negligible mortality of appendectomy in the uncomplicated acute stage of the disease. It is equally difficult to follow the reasoning of those who maintain that the world is flat.

Surgical technique made tremendous strides between 1890 and 1905, so much so that few, if any, basic technical changes have occurred since. The lower median and paramedian incisions were already known, and the classical incisions of McBurney,[31] Battle[2] (also variously known as the Kammerer,

Jalaguier, or Lennander[26] incision) and Rockey soon made their appearances. It is true that many modifications have been suggested by ambitious surgeons, but the variations have been of minor significance. During this period, two schools of thought arose concerning the disposition of the appendiceal stump, and techniques were evolved which are in use today, with but insignificant alteration. Basically, these are simple ligation, and inversion of the stump (or the entire appendix) into the cecum with or without preliminary ligation. A complication of the ligation-inversion technique was reported as early as 1901 by Herman.[18] Unlike the eponymous incisions, none of the methods of stump disposal have brought lasting fame to their discoverers, and determination of actual priority is well-nigh impossible.

There is no longer the dearth of surgeons capable of operating for appendicitis, nor of hospitals in which to operate, which led Finney, Kelly and others to describe traveling kits for the performance of appendectomy far from metropolitan centers. In fact, the criticism has been raised that too many operators are all too willing to remove the appendix for little or no reason. This criticism was not unfounded, as the appendix came to be considered the source of almost every medical evil, and its removal suggested as a cure for ailments as diverse as arthritis and melancholia. Few of these claims stood the test of time, and today are buried in the vast accumulation of literature which has grown up around appendicitis. Even "chronic" appendicitis is rarely considered a source of disease by astute clinicians today. During the second and third decades of this century, chronic appendicitis became almost fashionable, and appendectomy was undoubtedly the operation flayed by George Bernard Shaw in "The Doctor's Dilemma."

Since the two magnificent monographs on appendicitis by Kelly and Hurdon,[22] and by Sprengel,[52] which appeared in 1905 and 1906 respectively, the literature has mounted to astronomical proportions. Sprengel cited approximately 5,400 references, and 13,621 articles have appeared since 1886, according to Hawk and associates.[17] A random sample, 1936-1946, in the Cumulative Index, shows 3,600 titles cited under appendicitis alone. Although the minutest variations of disease, diagnosis, and treatment have been recorded, there is comparatively little radically new, or different from the teachings of Murphy, Ochnsner, or Moynihan, to mention but a few of the pioneers in the modern treatment of appendicitis. The present low mortality is due in all probability to the continuing efforts of surgeons the world over, preaching the gospel of early diagnosis and early operation.

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Erratum

On page 465 of the September, 1951, issue, in the article "Extensive Resection of the Small Intestine Followed by Vagotomy" by Elden C. Weckesser, Jay L. Ankeney, A. Frank Portmann, J. Waide Price, and Frank A. Cebul, the italics line under the authors' names should read:

(From Departments of Surgery and Pathology, Western Reserve University and University Hospitals)

instead of Western Kansas University.

Book Reviews

Acute Head Injury. By J. P. Evans, M.D., Ph.D., Associate Professor of Surgery, Director of Division of Neurological Surgery, University of Cincinnati College of Medicine, Cincinnati, Ohio. Pp. 116, with 24 illustrations. Springfield, Ill., 1949, Charles C Thomas, Publisher. $7.00.

This monograph is a rather routine review of the experimental and clinical problems of acute head injuries. It is distinguished by the inclusion of the author's personal cases and his free discussion of them. He presents clearly and understandably the various syndromes of head injuries and follows these with a discussion of the physiology and pathology involved. The rationale and details of therapy are given. The monograph is well illustrated. It has a good bibliography.

This book is recommended for physicians in general practice as well as for specialists.

Post-Graduate Lectures on Orthopedic Diagnosis and Indications, Vol. II. By Arthur Steindler, M.D., F.A.C.S., Professor of Orthopedic Surgery, State University of Iowa, Iowa City, Iowa. Pp. 208, with 209 illustrations. Springfield, Ill., 1951, Charles C Thomas, Publisher. $6.00.

This, the second volume of the series, maintains the same high standard of presentation set by Volume I. However, a brief correlation of the table of contents with the length of the book (198 pages) reveals that an adequate review of the many subjects catalogued is impossible in this short space. As a set of lecture notes and as a framework for further study the book fulfills its purpose, but it is nothing more.

Die Gynäkologischen Operationen. (Translation: "Gynecological Operations and Their Basic Topographical Anatomy"). By Dr. Heinrich Martius, Director of the Gynecological Clinic of the University of Göttingen, Germany. Ed. 6, 1950, George Thieme verlag, Stuttgart.

This publication by one of the outstanding German gynecologists is the sixth edition in a series which began in 1936. It has been considerably revised since the fifth edition, subsequent to a review of the newer literature accessible to Germany since the last war.

It is a commendable effort, which offers a fairly complete presentation of the technique of most of the recognized gynecological operations as performed by the German school, combining excellent illustrations, both technical and anatomical, with an adequate written description. Unfortunately, the printing of the text, which is in German, is not up to American standards, and makes reading more difficult.

The discussion of the indications for the various surgical procedures is limited, and some of the ideas and surgical preferences are probably not in accord with those of a majority of American gynecologists. The author still prefers subtotal over total hysterectomy, except in cases of carcinoma and severely diseased cervices. This is perhaps justified in his experience, because he gives his operative mortality as 7.8 per cent for total hysterectomy as compared with 1.6 per cent for subtotal. These rates are remarkably high when compared with those recently published from recognized gynecology centers in this country. The problem of surgery in the treatment of carcinoma of the uterine cervix and fundus could have been more clearly and adequately presented.

It is interesting to note the considerable amount of space devoted to the various types of genital fistulas. This may be because the Europeans possibly still see a greater number of fistulas today than do the Americans.

This book can be recommended as a fine technical and anatomical aid for the gynecological surgeon, but not as a textbook for students of the subject.

Clinical Uses of Intravenous Procaine. By David J. Graubard, M.D., and Milton C. Peterson, M.D., New York Post Graduate Medical School and Hospital, New York, N. Y. Pps. 104, with few illustrations. Soft. Price $2.25. Springfield, Ill., Charles C Thomas, Publisher. 1950.

This monograph is well written and covers very completely the fields in which intravenous procaine has been used. It is evident that the judicious use of procaine is useful for many situations, such as pain associated with changing of dressings and burns, pruritus, serum sickness, painful traumatic and inflammatory conditions. The authors have also been careful to indicate the limitations and dangers associated with the uses of intravenous procaine. This monograph can be recommended highly and will find a useful place in the library of anesthetists and internists as well as surgeons.

La Craniectomia a Traves de los Siglos. By Rafael Vara Lopez. Valladolid, 1949, Discurso de Apertura del Curso de 1949-1950 de la Universidad de Valladolid.

This is an excellent review of the history of craniectomies and/or craniotomies. It is well documented and scholarly written. Although the author is a general surgeon and not exclusively a neurosurgeon his command of the subject reveals him as a broadly educated man. The reading of this book will be of interest to neurosurgeons, general surgeons, and neurologists who wish to look into this part of the historical background of neurosurgery either to satisfy a plain curiosity or in an attempt to learn from the past.

Proceedings of the First Annual Symposium on Orthopedic Appliances. Under the auspices of the Sarah Mellon Scaife Foundation's Multiple Fellowship at Mellon Institute and the Department of Orthopedic Surgery, School of Medicine, University of Pittsburgh. Pp. 308, with few illustrations. Washington, D. C., 1950, Issued by the Orthopedic Appliance and Limb Manufacturers Association. $5.00.

These proceedings are a record of lectures and discussions dealing with the principles and the technical problems included in the construction and fitting of orthopedic appliances. Various braces are illustrated and the significant points in their design are pointed out. Such material is of interest mainly to the bracemaker and to physicians prescribing orthopedic appliances, and for them this book forms a compendium of useful information.

Plasma Clot Suture of Peripheral Nerves and Nerve Roots. By J. M. Tarlov, M.D., Associate Professor of Neurosurgery, New York Medical College, New York City, Pp. 116, with 46 illustrations. Springfield, Ill., 1950, Charles C Thomas, Publisher. $2.25.

This book is a concise discussion of the most recent methods of repairing severed nerves. It contains an evaluation of previous methods of repairing nerves and proposes this newer method, namely the plasma clot suture. There is a very thorough verbal and graphic discussion of the latter technique. The exact procedure as used by Dr. Tarlov is shown and several minor modifications of his method are discussed. That the plasma clot technique is not as yet entirely satisfactory is evidenced by the necessity of using tantalum wire tension sutures in combination with the plasma clot. This is not particularly stressed in the book. However, this technicality does not detract from the author's excellent presentation of his clinical and experimental work. Included in the monograph are discussions of simple end-to-end anastamoses of peripheral nerves, peripheral nerve grafts, and free grafting of the roots of the cauda equina. No one can question that this is a most complete review of the subject by its most eminent authority. This book should be in the library of everyone interested in peripheral nerve injuries.

The Practice of Urology. By Harry C. Rolnick, M.D., Cook County Hospital, Chicago, Ill. Vol. I, pp. 616, Vol. II, pp. 1,245, with many illustrations. Philadelphia, Pa., 1949, J. B. Lippincott Company, $24.00.

This two-volume textbook on urology is a much needed adjunct to the library of a student or graduate of medicine. The work includes important progress made during the past several decades in the treatment of infections, hormonal therapy, aids in diagnosis, and improvements in surgical techniques.

The contents are readable, and presented in an orderly manner. The drawings and reproductions are excellent. The basic subjects in the text are especially well presented for the clinician: embryology, anatomy, physiology, instruments, laboratory methods, and radiography.

The reviewer suggests that the references could have been arranged in a more convenient manner at the end of each chapter. The section on venereal diseases occupies a large space for the modern urologist; this is perhaps of more value to the general practitioner or medical student.

The chapters on technique of urologic procedures are well illustrated and easily interpreted. From the urologist's point of view, a little more detail could have been included in describing operations on hypospadias, cryptorchism, and ureteropelvic junction obstructions.

The four popular operations for the relief of prostatic obstruction are well presented except that the authors take little heed of the importance of using isotonic solutions during transurethral resection of the prostate. The descriptions of retropubic and suprapubic prostatectomies are excellent.

The section on urology in children is not inclusive enough to be of value to the urologist. The chapters on infections, anomalies, injuries, urology in the female, and stricture of the urethra are superb.

The reviewer believes that the *The Practice of Urology* will provide the medical student and general practitioner with a much needed textbook in a field which has progressed beyond the scope of books published more than a decade ago. For the urologist, it seems that the references and certain operative techniques might have been more inclusive and detailed. However, it was probably not Dr. Rolnick's aim to compile the text solely for the convenience of specialists in urology.

In summary, many will concur with the reviewer that Dr. Rolnick's textbook is the most desirable modern work on urology available to date.

Cerebral Palsy. By John F. Pohl, M.D., Orthopedic Surgeon, Michael Dowling School for Crippled Children, Minneapolis, Minn. Pp. 224, with 131 illustrations. St. Paul, Minn., 1950, Bruce Publishing Company. $5.00.

This small book is devoted primarily to the methods of retraining children with cerebral palsy. The first chapter is concerned with the medical problem, including, as it must, some discussion of the variations and nature of the brain injury and the resulting clinical syndromes.

Unfortunately, a number of statements regarding the anatomy, physiology, and clinical symptoms in this section are loosely made and definitely inaccurate. If this book is directed at the physicians, then such inaccuracies naturally are unjustified. However, if this work is directed chiefly at the lay public or for nonmedical readers, then perhaps one can justify many of these inaccuracies as a means of simplification of a most complicated subject. Fortunately most of the book is devoted to the methods of retraining children with cerebral palsy. The descriptive techniques are fairly well done and the illustrations are well chosen. From a treatment standpoint, this small volume may prove useful particularly to the physical therapist and those dealing with the actual treatment procedures in the brain-damaged child.

Modern Trends in Orthopaedics. By Sir Henry Platt, M.D., M.S., F.R.C.S., Professor of Orthopaedic Surgery, University of Manchester. Pp. 497 with many illustrations. Hard. New York, N. Y., 1950, Paul B. Hoeber, Inc., $10.00.

The title of this collection of articles on a variety of orthopedic conditions by a group of British authors is a misnomer in that in some respects it is at least five years behind current practices in the United States. This is most evident in the lack of a thorough discussion of the use of antibiotics, other than penicillin, in the treatment of tuberculosis and osteomyelitis. The Kenny concept of the treatment of acute poliomyelitis, so important in this country, is cursorily dismissed with a word. However, as a review of standard practices in Great Britain, this book can be read with interest and profit by the orthopedic specialist able to select the wheat from the chaff.

Orthopaedic Surgery. By Walter Mercer, M.B., Ch.B., F.R.C.S. (Edin.), F.R.S. (Edin.), Professor of Orthopaedic Surgery, University of Edinburgh, Director of Orthopaedic Services to the South Eastern Regional Hospital Board, Scotland. Pp. 1016, with 427 illustrations. Ed. 4. Baltimore, Md., 1950, Williams & Wilkins Company. $10.00.

This book is the best textbook concerning orthopedic subjects currently available. Carefully prepared, well illustrated, and reasonably priced, it should find a place in the libraries of many physicians, especially pediatricians, as a reference and aid in properly diagnosing many puzzling cases. The various diseases are discussed with special attention to differential diagnois and the indications for treatment. The results associated with various forms of treatment are given when available. The book could be shortened somewhat by eliminating the descriptions of the operative procedures since they can only be presented adequately in textbooks of operative surgery.

Books Received

The receipt of books is acknowledged in this section and this treatment must be regarded as sufficient acknowledgment of the courtesy of the senders. Selections will be made for more extensive review dictated by the interest of our readers as space permits.

THE HUMAN COLON. By William J. Grace, M.D., Assistant Professor of Medicine, Cornell University Medical College, New York Hospital, N. Y., Stewart Wolf, M.D., Cornell University Medical College, New York Hospital, and H. G. Wolff, M.D., Professor of Medicine (Neurology), Cornell University Medical College, New York Hospital. Price $7.50. Pp. 239, with 112 illustrations. New York, 1951, Paul B. Hoeber, Inc.

LUMBAR PUNCTURE AND SPINAL ANALGESIA. By R. R. MacIntosh, M.A., D.M., F.R.C.S., D.A., Nuffield Professor of Anaesthetics, University of Oxford, Fellow of Faculty of Anaesthetists, Royal College of Surgeons. Price $4.50. Pp. 148, with 111 illustrations. Baltimore, 1951, Williams & Wilkins Company.

ANGEWANDTE UND TOPOGRAPHISCHE ANATOMIE. By Dr. G. Tondury, Zurich, Switzerland. Price $16.65. Pp. 416, with 369 illustrations. Stuttgart, 1951, Grune & Stratton, Inc.

LEHRBUCH DER RONTGENDIAGNOSTIK. By H. R. Schinz, W. E. Baensch, E. Friedl, E. Uehlinger, Funfte, vollig new bearbeitete und vermehrte Auflage. Pp. 1920, 2676 illustrations. Stuttgart, 1951, Grune & Stratton, Inc.

CHLOROFORM—A STUDY AFTER 100 YEARS. By Ralph M. Waters, M.D., University of Wisconsin, Madison, Wis. Price $2.75. Pp. 338, with 32 illustrations. Madison, Wis., 1951, University of Wisconsin Press.

CONTRIBUTIONS OF SURGERY TO PREVENTIVE MEDICINE. By Sir James Learmonth, Regius Professor of Clinical Surgery and Professor of Surgery, University of Edinburgh. Price $2.50. Pp. 55, no illustrations. New York, 1951, Oxford University Press.

ANNUAL REVIEW OF MEDICINE. By many authors. Price $6.00. Pp. 485, with no illustrations. Stanford, Calif., 1951, Annual Review, Inc.

FORTSCHRITTE IN DER BEHANDLUNG SCHWERER UND SCHWERSTER HOCHSPANNUNGSUNFALLE. By Professor Dr. Med. H. Fischer and Dr. Med. R. Frohlicher, Zurich. Price DM 10.80. Pp. 71, with 23 illustrations. Stuttgart, 1951, Grune & Stratton, Inc.

CYSTEKTOMIE BEIM BLASENKREBS. By Prof. Dr. H. Boeminghaus, Dusseldorf. Price DM 11.50. Pp. 84, with 56 illustrations. Stuttgart, 1951, Grune & Stratton, Inc.

ANATOMY IN SURGERY. By Philip Thorek, M.D., F.A.C.S., F.I.C.S., Assistant Clinical Professor of Surgery, University of Illinois College of Medicine, Diplomate of the American Board of Surgery, Associate Professor of Topographic Anatomy and Clinical Surgery, Cook County Graduate School of Medicine, Chicago, Ill. Pp. 970, with 720 illustrations. Philadelphia, 1951, J. B. Lippincott Company.

CLINICAL UNIPOLAR ELECTROCARDIOGRAPHY. By B. S. Lipman, A.B., M.D., Assistant in Medicine, Emory University School of Medicine, Atlanta, Ga., and Edward Massie, A.B., M.D., F.A.C.P., Assistant Professor of Clinical Medicine, Washington University School of Medicine, Director of Heart Station, Barnes Hospital, St. Louis. Price $5.00. Pp. 232, with 191 illustrations. Chicago, 1951, The Year Book Publishers, Inc.

PRINCIPLES AND PRACTICE OF SURGERY. By J. K. Berman, A.B., M.D., F.A.C.S., Associate Professor of Surgery, Indiana University School of Medicine, Associate Professor of Oral Surgery, Indiana University School of Dentistry, Chief Consultant in Surgery, Billings Veterans Administration Hospital, Ft. Benjamin Harrison, Indiana, Director Surgical Education and Surgical Research, Indianapolis General Hospital, Indianapolis, Ind. Price $15.00. Pp. 1378, with 429 illustrations. St. Louis, 1950, The C. V. Mosby Company.

MEISTER DER CHIRURGIE UND DIE CHIRURGENSCHULEN IM DEUTSCHEN RAUN. By Professor Dr. H. Killian, Freiburg, and G. Kramer, Karlsruhe. Price DM 24.80. Pp. 230, with few illustrations. Stuttgart, 1951, Grune & Stratton, Inc.

VISCERAL RADIOLOGY. By Emerik Markovitz, M.D., formerly Head of Radiologic Department of Elizabeth Hospital of City of Budapest, Post-Graduate Lecturer at Central Radiology Institute of University of Budapest, Radiologist of Steiner Cancer Clinic, Atlanta, Ga. Price $24.00. Pp. 612, with 682 illustrations. New York, 1951, The Macmillan Company.